Sucrose ester stearates,

amphiphilic matrix systems for the formulation of sustained release preparations

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Abbreviations

API	Active pharmaceutical ingredient
AUC	Area under the curve
c_{min}	Minimum of all maximal chord lengths of a particle
CSP	CSP technologies, Packing vial with integrated molecular sieve, specified in 2.1.8 Packing materials
DDS	Drug delivery system
DSC	Differential Scanning Calorimetry
Fe_{max}	Maximum Ferret diameter of a particle
GRAS	Generally recognized as save
HLB	Hydrophilic Lipophilic Balance
HPC	Hydroxypropyl cellulose
HPLC	High performance liquid chromatography
HPMC	Hydroxypropyl methylcellulose
LC	Liquid crystal
L/D ratio	Length/Diameter ratio
LOD	Loss on drying
MCC	Microcrystalline cellulose
MRI	Magnetic Resonance Imaging
NMR	Nuclear Magnetic Resonance spectroscopy
p_3	Fractions of number density of particles, %

Ph.Eur.	European Pharmacopoeia 6th edition
POM	Thermal polarised light microscopy
PST	Primary standard
Q_3	Sum of number density of particles, %
RDA	Recommended Daily Allowances
r.h.	Relative humidity
RT	Room temperature
S-370	Sucrose ester stearate HLB 3
S-570	Sucrose ester stearate HLB 5
S-770	Sucrose ester stearate HLB 7
S-1170	Sucrose ester stearate HLB 11
S-1670	Sucrose ester stearate HLB 16
SE	Sucrose ester
SMCC 50	Silicified microcrystalline cellulose, average particle size 60 µm
SMCC 90	Silicified microcrystalline cellulose, average particle size 110 µm
SPHT	Sphericity
TCP	Tricalcium phosphate
T_G	Glass transition temperature
USP	United States Pharmacopoeia 31
WST	Working standard

1 Introduction

New excipients for solid dosage forms are always of great interest either to provide the characteristics of the drug product or to improve bioavailability of the API. In the focus are natural or synthetic substances which are biocompatible and biodegradable into non-toxic products [1,2]. Sucrose esters (SE) are a group of excipients well-known for their use in semisolid dosage forms. They are widely used in cosmetic and food industries as stabilizers, surfactants and lubricants in ice cream, bread, cakes, candy, pasta products or chocolate. The potential of SEs for pharmaceutical use is known for different applications, e.g. as solubility enhancers [3], surfactants [2,4], lubricants [5] or as crystal growth inhibitors [6]. However, SEs can also be used in new innovative applications as nanodispersions [7], microemulsions [8-10], transdermal therapeutic systems [11] or as absorption enhancers [12]. It is also known that SEs can be applied in classical pharmaceutical solid dosage forms but little scientific work has been done on that topic. The function as lubricants is recommended by the manufacturer [5], but it is also known that SEs can be used as controlling agents for sustained release formulations [13-15]. There are sustained release products on the market containing SEs as matrix forming agents and ibuprofen or Bunazosin HCl as the active substance [16]. But no scientific information can be found describing the properties and application range of SE as matrix forming agents.

The function as matrix formers and the application range of SEs in different solid dosage forms was investigated and is described in this thesis. Different solid dosage forms were tested. For HPMC as matrix formers an enormous range of publications is available describing their pharmaceutical technological application, release mechanism and compare the different types of HPMC with each other. For SEs this information is not available. Especially the application in different solid dosage forms, the release mechanism and the comparison to other matrix formers is not published yet. Matrix forming mechanism and matrix properties are not described. This thesis will cover these investigations to show the potential of SE application in solid dosage forms.

The characteristics of commercially available SEs or even of their pure substances are not fully understood. Furthermore, SE preparations on the market are always mixtures of different SEs which differ in the number of esterifications, the kind of fatty

acids or the composition of the mixture. This makes a good description of the material much more complicated but represents a natural mixture of ester which is usually formed during storage by ester interchange. Using these mixtures the stability is expected to be good and no alteration of release patterns during storage should occur. The composition of the mixtures determines the characteristics in thermic behavior, dissolution of active ingredients and texture formation. To give an overall description of SEs in general the available number of products is much too high. The focus of this work was set on stearic acid as the main fatty acid in the product (Figure 1) because for this SEs a wide range of HLB values are available on the market. These SE types also have the advantage to be nearly tasteless and therefore good acceptance of the consumer is expected.

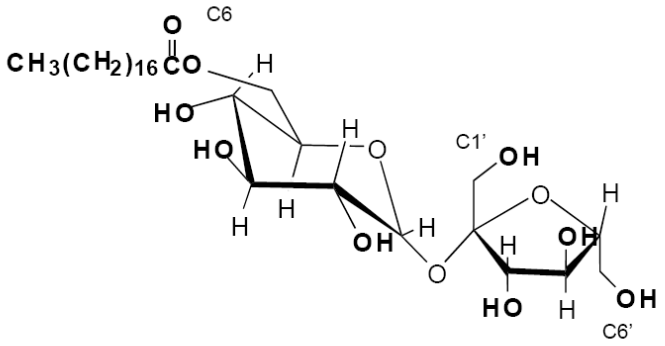


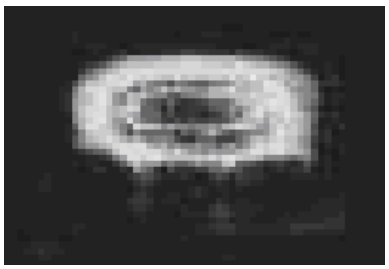
Figure 1. Chemical structure of sucrose monostearate.

Release kinetics from different dosage forms can be determined through mathematical modelling. The history of quantitative consideration of drug release from pharmaceutical dosage forms is not very long [17]. The start of this scientific investigation can be set to the publication of Higuchi's equation in 1961 which described the drug release from an ointment base. Computer simulation can provide a better understanding of the system used which can lower the number of experiments and therefore lower the costs of development when working with new APIs or rarely known excipients. Many different models have already been published and can be used to describe release processes from dosage forms [17]. In this study a mechanistic realistic model based on the phenomenon of diffusion described by

Fick's second law was used to describe the release mechanism of the active substances form the tested dosage forms.

Vitamins are often used to simulate the active ingredients in matrix systems. B vitamins are a very heterogenic group of substances and therefore provide the opportunity to describe the matrix behavior and release kinetics of different APIs from SE-based matrices very well. The impact of the manufacturing process on the assay of the active ingredient can be described as well because some of the vitamins used are very sensitive to heat or light. Using mathematical modelling, the different structures of the vitamins and their release kinetics can be compared to determine whether water solubility, molecular mass or only the matrix formation influences the release kinetics of vitamins from the system. This knowledge can also help to estimate the release of other substances from SE-based systems.

Invasive and non-invasive imaging techniques were applied in order to describe the matrix forming behavior. Optical light macroscopy and NMR imaging (MRI) were used to determine matrix forming and water uptake behaviour into the matrix system. In pharmaceutical research MRI is used to determine hydration, swelling or erosion processes in dosage forms during dissolution testing [18,19]. During dissolution the different zones of water penetration and polymer gel formation can be detected (Figure 2), but MRI can be also be used to monitor the in vivo performance of drug delivery systems [20].



Dark, core:	dry tablet core
White, inner layer:	water penetrated region
Dark, inner layer:	stiff gel layer
White, outer region:	soft gel layer
Dark, outer region:	Glass spheres and medium

Figure 2. MRI of a HPMC-based tablet after 50 min in phosphate buffer, flow through cell.

The aim of this work was the development of sustained release matrix systems based on SEs. Scientific investigation on SEs matrix systems was carried out to close the gap of knowledge in comparison to HPMC matrices. It was elucidated if SEs can be used in multi-particulate systems as well as in monolithic dosage forms. Galenical limitations or risks in the use of these excipients were discovered. The influence of different manufacturing methods on the performance of the matrix systems was investigated. Limitations to several SE types, dosage forms or manufacturing methods were determined. These investigations will close the gap of investigation on SEs as matrix forming agents.

2 Materials and Methods

2.1 Materials

2.1.1 Sucrose esters (SE)

SEs are well-known as non-ionic, non-toxic and odourless surfactants in food and cosmetic industries. Especially the stearate esters cover a large range auf HLB values [21] depending on the number of esterifications. The stearates are tasteless and are therefore suitable for pharmaceutical use. SEs are approved food additives if they contain more then 70 % mono- and diesters in the substance (E473 sugar esters of fatty acids) and can also be purchased in pharmaceutical grade. All SE products used were food grade because of their use in nutritional supplements. SEs are able to form matrix tablets using direct compression or wet granulation. The amount of SE influences the release rate from the matrix as well as thermal treatment of the granules before compression into tablets [13,14]. Due to their low melting ranges SEs can also be used in melt granulation and hot melt extrusion technologies [14]. However, their low melting ranges (Table 1) can also limit their use in pharmaceutical preparations to climate zones I and II. In the literature there is no information on the use of SEs as matrix forming agents in controlled release multi-particlulate systems. The characteristics of SEs haven’t been completely understood but are being investigated increasingly [7,22,23]. Commercially available SE materials are mixtures of different esters (Table 1). Therefore it is difficult to determine several parameters e.g. the melting point of the substance. Melting ranges can be determined due to the SE mixtures. These wide melting ranges are assumed

to cover a glass transition [21]. The mixtures are an advantage in the case of storage stability. During storage ester interchanges occur and can alter the release patterns of a preparation. Within the mixtures the natural ester distribution is given from the beginning and during storage not significant changes are expected. It should also be taken into account that SEs form thermotropic and lyotropic liquid crystalline mesophases [24-28]. Additionally, the lyotropic and thermotropic behavior can influence the matrix forming of SE based matrices. Chapter 3.1.2 describes this phenomenon in detail. Hence, SEs are sensitive to thermal treatment. The time of recrystallisation can have an impact on functionality of the dosage form and consequently on the stability of the system. In order to provide a secure and well-known drug product these characteristics of raw materials should be well understood before starting the development process.

Table 1. Characteristics of applied sucrose ester types [MSDS]

Substance	**Sucrose ester stearate S-370**
HLB number	3
Synonym	Ryoto® Sugar Ester S-370
Supplier	Mitsubishi-Kagaku Foods Corp., Tokyo, Japan
Melting range	51 - 69 ℃
Composition of substance	Sucrose - monostearate 12 - 14 % - distearate 21 - 23 % - tristearate 19 - 21 % Also contains tetrastearate and pentastearate and other alkyl esters. In total: >70 % stearate esters

Substance	**Sucrose ester stearate S-570**
HLB number	5
Synonym	Ryoto® Sugar Ester S-570
Supplier	Mitsubishi-Kagaku Foods Corp., Tokyo, Japan
Melting range	50 - 65 ℃
Composition of substance	Sucrose - monosterate 18 - 20 % - distearate 23 - 25 % - tristearate 15 - 17 % Also contains tetrastearate. In total: >70 % stearate esters

Substance	**Sucrose ester stearate S-770**
HLB number	7
Synonym	Ryoto® Sugar Ester S-770
Supplier	Mitsubishi-Kagaku Foods Corp., Tokyo, Japan
Melting range	49 - 60 ℃
Composition of substance	Sucrose - monostearate 25 - 26 % - distearate 22 - 23 % - tristearate 12 - 13 % Also contains tetrastearate. In total: >70 % stearate esters

Substance	**Sucrose ester stearate S-1170**
HLB number	11
Synonym	Ryoto® Sugar Ester S-1170
Supplier	Mitsubishi-Kagaku Foods Corp., Tokyo, Japan
Melting range	49 - 55 ℃
Composition of substance	Sucrose - monostearate 37 - 39 % - distearate 20 - 22 % Also contains tristearate. In total: >70 % stearate esters

Substance	**Sucrose ester stearate S-1670**
HLB number	16
Synonym	Ryoto® Sugar Ester S-1670
Supplier	Mitsubishi-Kagaku Foods Corp., Tokyo, Japan
Melting range	49 - 56 ℃
Composition of substance	Sucrose - monostearate 50 - 53 % - distearate 12 - 14 % Also contains tristearate. In total: >70 % stearate esters

2.1.2 Vitamins

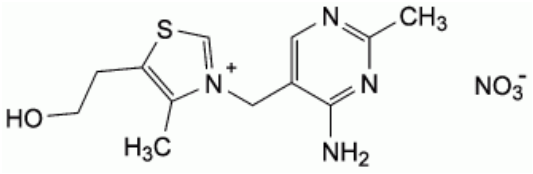
B vitamins are essential for several functions in the human body. All vitamins used, (nicotinamide, pyridoxine, riboflavin and thiamine) act as coenzymes [29-34] in the regulation of nerval functions, in amino acid metabolism and are energy vectors in the respiratory chain. Vitamins are often used as drugs or model drugs in pharmaceutical applications. Nicotinic acid can be used as a hyperlipidaemic or as a

model drug [35-38]. Also riboflavin and its derivates are often used as model drugs [39-41] due to the low toxicity and highly heterogenic chemical structures. The different molecular weight and water solubility (Table 2) of the substances offer the investigation of the impact of these parameters without using drugs with higher toxicity. The dosage level of vitamins in nutritional supplements is very similar to many drugs. Therefore comparable levels are used and allow a prognosis of the behavior of other drugs in the same matrix system. In this study the dosage level followed the RDA of the European council 1990 [42]. This directive was amended in 2008 [43]. For better comparison of data the former dosage levels of 1990 were kept during the studies. Vitamins are only absorbed in the small intestine. In the colon the absorption of vitamins is negligible. All used vitamins can be absorbed in the whole small intestine with decreasing absorption rates from the duodenum towards the colon. The transition time through the small intestine therefore determines the maximum dissolution time of the developed sustained release formulation.

Many vitamins are sensitive to light and humidity, which is why all analytical determinations were carried out protected from light in order to prevent vitamin loss during the analysis. Nutritional supplements often comprise mixtures of vitamins. For the determination of matrix effects nicotinamide, pyridoxine, riboflavin and thiamine were added simultaneously to the formulations. These four vitamins are excellent examples to describe the impact of the manufacturing process on the actives because of their different physicochemical properties. Nicotinamide tolerates heat and light very well and can be used as the tracer for a very stable structure. Pyridoxine and riboflavin are very sensitive to light and heat. Thiamine is also sensitive to heat and additionally to oxygen but stable to heat (See Annex Figure 1A). The sensitivity of the vitamins to these influences is much higher in solution than in the solid state. In order to guarantee the stability of the substances during the dissolution in phosphate buffer the dissolution time was limited to a maximum of 8 hours (The stability over 4 h is shown in Annex Figure 2A). Vitamin C and pantothenic acid were used for the development of a three layer tablet formulation (Chapter 7). These studies can also help to provide a better comprehension of the release behavior of different vitamins and vitamin salts in solid dosage forms.

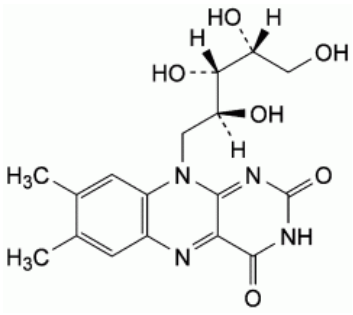
Table 2. Characteristics of applied vitamins [29-33].

Vitamin	RDA	Vitamin salt	Molecular weight	Solubility in H_2O	Supplier
Vitamin B_1	1.4 mg	Thiamine cation	265.35 Da	-	-
		Thiamine nitrate	327.36 Da	27 g/L	DSM, Basel, Switzerland
		Thiamine chloride hydrochloride	337.28 Da	1000 g/L	DSM, Basel, Switzerland

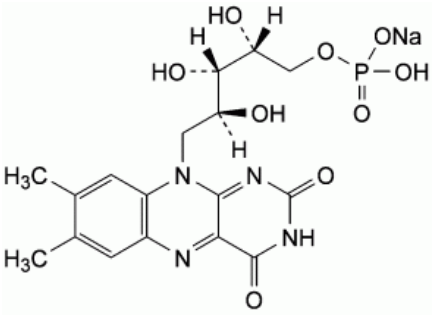


Thiamine nitrate

Vitamin	RDA	Vitamin salt	Molecular weight	Solubility in H_2O	Supplier
Vitamin B_2	1.6 mg	Riboflavin	376.37 Da	0.07 g/L	BASF, Ludwigshafen, Germany
		Riboflavin 5’-phosphate	478.33 Da	112 g/L	DSM, Basel, Switzerland

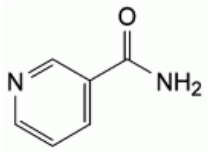


Riboflavin



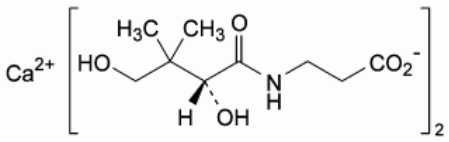
Riboflavin 5’-phosphate

Vitamin	RDA	Vitamin salt	Molecular weight	Solubility in H_2O	Supplier
Vitamin B_3	18 mg	Nicotinamide	122.13 Da	~1000 g/L	DSM, Basel, Switzerland



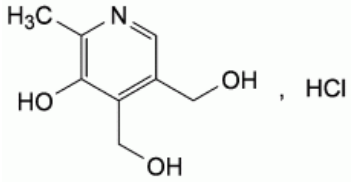
Nicotinamide

Vitamin	RDA	Vitamin salt	Molecular weight	Solubility in H_2O	Supplier
Vitamin B_5	6 mg	Calcium pantothenate (Pantothenic acid)	476.54 Da (219.0 Da)	375 g/L	DSM, Basel, Switzerland



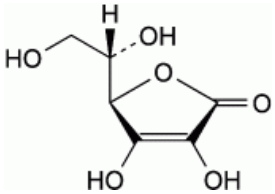
Calcium pantothenate

Vitamin	RDA	Vitamin salt	Molecular weight	Solubility in H_2O	Supplier
Vitamin B_6	2 mg	Pyridoxine H^+	170.18 Da	-	-
		Pyridoxine hydrochloride	205.64 Da	~220 g/L	DSM, Basel, Switzerland



Pyridoxine hydrochloride

Vitamin	RDA	Vitamin salt	Molecular weight	Solubility in H_2O	Supplier
Vitamin C	80 mg	Ascorbic acid	176.1 Da	300 g/L	DSM, Basel, Switzerland



Ascorbic acid

2.1.3 Lipid matrix formers

Lipid matrices are often used in pharmaceutical preparations to sustain the release of drugs [44-47]. Glycerol dipalmitostearate (HLB = 2, melting point: 56 °C) and glycerol behenate (HLB = 2, melting point: 70 °C) were provided by Gattefossé, Saint-Priest Cedex, France. Both excipients are suitable for sustained release preparations. These excipients were chosen to compare the behavior of SEs with lipid matrix formers.

2.1.4 Hydrophilic matrix formers

Hydrophilic matrix formers extend the release of APIs from the dosage form through extreme swelling and the formation of a hydrogel with high viscosity in the outer layer of the dosage form. HPMC, HPC, polyacrylic acid, alginate or chitosan are commonly used in pharmaceutical preparations. The matrix forming mechanism of those systems is described in many publications [38,48-56]. Hydrogel matrix formers are suitable for sustained release preparations of substances with a wide variety of physico-chemical properties [49,57], but are not able to sustain the release of good soluble substances from granules due to the short diffusion pathway or a fast moving erosion front. These systems are widely used and well-known in pharmaceutical preparations and are therefore a good example to compare the behavior of SEs with those matrix formers.

Table 3. Characteristics of applied hydrogel matrix formers

Substance	Viscosity	Synonym	Supplier
Hydroxypropyl cellulose (HPC)	1,500 - 3,000 cps (1%) 25℃	Klucel HXF	Ashland, Hopewell, VA, USA
Hydroxypropyl methylcellulose (HPMC)	100,000 cps (USP Ubbelohde)	Benecel MP844	Ashland, Hopewell, VA, USA
Polyacrylic acid	4,000 - 11,000 cP. 0.5%	Carbopol 971P NF	Noveon Europe BVBA, Brussels, Belgium

2.1.5 Excipients

The following excipients were used in the formulations as filling agents or lubricants and were purchased from the indicated suppliers.

Table 4. Excipients used in different formulations.

Substance	Product	Supplier
Microcrystalline cellulose	Avicel PH102 Avicel PH200	FMC biopolymer, Cork, Ireland
Ethyl cellulose	T10 PHARM	Ashland, Aqualon Division, Hopewell, VA, USA
Tricalcium phosphate	TRI-CAFOS S	Budenheim, Germany
Starch	Cerestar C*Pharm	Cargill, Krefeld, Germany
SMCC 50	SMCC 50	JRS Pharma, Rosenberg, Germany
Glucose monohydrate		Merck KGaA, Darmstadt, Germany
PEG 6000		Merck KGaA, Darmstadt, Germany
Magnesium stearate	MF-2-V veg.	Peter Greven, Venlo, Netherlands

2.1.6 Reagents for analysis

Table 5. Reagents used in the studies.

Substance	Art.Nr.	Supplier	Used as
Potassium dihydrogen phosphate, KH_2PO_4	1.04873	Merck KGaA	HPLC analysis: Mobile phase; Dissolution medium
Heptan-1-sulfonic acid sodium, Ion pair reagent	1.18306	Merck KGaA	HPLC analysis: Mobile phase
Triethylamine	8.08352	Merck KGaA	HPLC analysis: Mobile phase
ortho-Phosphoric acid 85%	1.00563	Merck KGaA	HPLC analysis: Mobile phase
Sodium hydroxide solution 1 mol/l, NaOH	1.09137	Merck KGaA	Dissolution medium
Hydrochloric acid 0.1 N, HCl	1.09060	Merck KGaA	Dissolution medium
Methanol, gradient grade, CH_3OH	1.06007	Merck KGaA	HPLC analysis: Mobile phase
Vitamin B_1, Thiamin nitrate	PST 500980	Merck KGaA	Reference standard
Vitamin B_1, Thiamin chloride hydrochloride	WST 500923 502062	Merck KGaA	Reference standard
Vitamin B_2, Riboflavin	WST 500257	Merck KGaA	Reference standard
Vitamin B_2, Riboflavin-5' phosphate sodium salt * 2 H_2O	PST 500259	Hofmann La Roche AG/ Merck KGaA	Reference standard
Vitamin B_6, Pyridoxine hydrochloride	WST 500224	Merck KGaA	Reference standard

Substance	Art.Nr.	Supplier	Used as
Vitamin $B_{3,}$ Nicotinamide	WST 502052	Merck KGaA	Reference standard
Acetonitrile, LiChrosolv gradient grade	1.00030	Merck KGaA	HPLC analysis: Mobile phase
di-Sodium hydrogen phosphate anhydrous, GR for analysis	1.06586	Merck KGaA	HPLC analysis: Mobile phase
Titriplex II, GR for analysis	108417	Merck KGaA	Stabilization of vitamin C in dissolution medium

2.1.7 Water

Ultra pure water for HPLC analysis was freshly prepared using an Astacus, membraPure, Bodenheim, Germany. For the preparation of dissolution medium purified water was used.

2.1.8 Packing material

To determine storage stability of the obtained preparations, the granules, pellets or mini tablets were packed into different packing material.

PP tubes: PP screw closure system containers were purchased from Cope Allman Jaycare Ltd., Portsmouth, UK.

CSP tubes: PP active vials white, M3028-127, containing molecular sieve as desiccant on the inner wall, were purchased from CSP technologies, Auburn AL, USA. Adsorption capacity: 2000 mg.

2.2 Methods

2.2.1 HPLC analysis

Different HPLC methods are known to simultaneously determine the content of water-soluble vitamins [58-61]. The analysis time of a well-known in-house method was too long for the number of analyses per day occurring during dissolution testing. It must be guaranteed that no vitamin degradation occurs during the time of analysis of all samples while using this method. A previously published method for the separation and UV detection of the vitamins ascorbic acid, nicotinic acid, nicotinamide, riboflavin 5'-phosphate, pyridoxine, riboflavin, folic acid and thiamine was used [62] and combined with the well-known in-house method to shorten the time of analysis. This combination enabled also the analysis of riboflavin 5'-phosphate which consists of more than 6 different riboflavin cofactors. The following shorter method was established and samples were analyzed for their vitamin contents by reversed phase ion pair exchange HPLC analysis (Hitachi Elite LaChrom) on a LiChrospher 100 RP-18e, 5 µm column (250 mm x 4 mm I.D.). For the mobile phase a buffer solution containing ~1.9 g/L sodium salt of heptansulfonic acid, ~1.5 g/L potassium dihydrogen phosphate, 5 mL/L triethylamine was produced. The pH was adjusted with phosphoric acid 85 % to pH value 2.4. The buffer solution was mixed and sonicated with methanol in a ratio of 4:1. Flow rate: 1.0 mL/min 0-10 min; 1.6 mL/min 10-22 min. The vitamins were detected by the UV detector at the following wave lengths in the indicated order: nicotinamide 264 nm, riboflavin 5'-phosphate 270 nm, pyridoxine 290 nm, riboflavin 270 nm, thiamine 250 nm. When free riboflavin was contained in the samples the flow rate was kept constant at 1.5 mL/min.

The determination of calcium pantothenate was carried out by HPLC analysis (Hitachi Elite LaChrom) on a PurospherStar RP-18e, 3 µm column (125 mm x 4 mm I.D.). For the mobile phase a buffer solution containing ~8.9 g/L di-sodium hydrogen phosphate was produced. The pH was adjusted with phosphoric acid 85 % to pH value 3.0. The buffer solution was mixed with acetonitrile in a ratio of 100:3. Flow rate: 1.2 mL/min. The vitamin was detected by a UV detector at 210 nm.
The determination of ascorbic acid was carried out by HPLC analysis (Hitachi Elite LaChrom) on a LiChrospher 100 RP-18e, 5 µm column (250 mm x 4 mm I.D.). For the mobile phase a buffer solution containing ~6.8 g/L potassium dihydrogen

phosphate was produced. The pH was adjusted with phosphoric acid 85 % to pH value 2.7. The buffer solution was mixed with methanol in a ratio of 100:3. Flow rate: 0.5 mL/min. The vitamin was detected by a UV detector at 243 nm.

For analysis of content and identification of the peaks pure vitamin reference substances (primary standards and working standards, Merck KGaA, Darmstadt, Germany) in ultra pure water were used. All analytical samples were prepared under the protection from light or transferred into brown glass devices as soon as possible after withdrawal from the vessels due to the sensitivity to light of pyridoxine hydrochloride, riboflavin and their cofactors.

2.2.2 Dissolution

Vitamin release from the different dosage forms was measured in 500 mL 0.1 M HCl, purified water or phosphate buffer pH 6.8 (Ph.Eur.) [63], using the USP 31 paddle apparatus [64] DT 80, Erweka, Heusenstamm, Germany (SE preparations) or Sotax AT7 smart, Allschwil, Switzerland (Three layer tablet formulations). The instruments were equipped with automatic sampling devices with fraction collector. 3 mL of dissolution medium were withdrawn from the vessel for analysis of vitamin content and not replaced with fresh medium. After withdrawal of the last sample the remained dosage forms were destroyed using an Ultra turrax® T25 basic, IKA-Werke, Staufen, Germany for determination of the total vitamin content of each dosage form. All analyses were carried out in triplicate. In all cases sink conditions were assured throughout the experiments.

2.2.3 Differential scanning calorimetry (DSC)

DSC measurements were carried out in a calorimeter DSC 200/1/F (Netzsch Thermal Analysis, Germany). Samples of approximately 3 - 7 mg were weighed and measured in balanced aluminium pans and compared to an empty reference pan. Two heating-cooling cycles with a temperature range starting from 5 °C to 90 °C (80 °C), respectively 200 °C with a heating and coo ling rate of 10 K/min were scanned under N_2 atmosphere. The temperature was held at the start and end point in each case for 5 min and then cooled or reheated again. The same cycles were scanned with a heating and cooling rate of 2 K/min. DSC is a well-known tool to

investigate and describe thermal processes in pharmaceutical preparations. In this study DSC was used to determine melting ranges, liquid crystalline phase transitions and recrystallisation behaviour of the different SE types. The determination of a glass transition temperature was not possible due to overlaying phase transition peaks.

2.2.4 Texture analysis

A texture analyzer is a very flexible tool for the analysis of different materials. A probe moves down onto the sample. The force, distance and time of the probe can be determined when penetrating into the sample. In pharmaceutical applications it is often used for the determination of breaking strength of films or the hydrated layer thickness of matrix tablets during dissolution [48,49,65-69]. The device can be used with different probes depending on the type of material tested. Compared to hydrogel matrices, SE matrices are very stiff. A cylindrical probe with a small diameter would not penetrate into the tablet. The water penetrated layers of the tablet would be compressed and would adulterate the analysis results. The needle probe is a good tool to analyse the layer thickness in SE matrices. Unfortunately the needle probe would not detect the penetration into a hydrophilic matrix tablet because the hydrogel is too soft, which is why a direct comparison of SEs and hydrogel matrix tablets is not possible using this method of analysis.

The hardness of granules was determined by using a TA.XT plus Texture analyzer, Stable Micro Systems Ltd., Godalming, Surrey, UK. The hardness was determined by the analysis of single granules using a flat-tipped cylindrical stainless steel probe, diameter: 6 mm, contact area: 28.27 mm², pre-test velocity: 1 mm/s, test velocity: 0.2 mm/s, post-test velocity: 0.2 mm/s, maximum force: 50.0 N, Trigger force: 0.005 N, load cell: 5 kg. The particle shape has a strong influence on the hardness of the granules which leads to high standard deviations but gives an impression on hardness differences. The strength of the matrix mini tablets was determined by the same method.

The hydration of the mini tablets during dissolution can also be followed using the texture analyser. The layer thickness of the hydrated layer was determined using a needle stainless steel probe, the contact area of the needle was defined 0 mm², pre-test velocity: 1 mm/s, test velocity: 0.2 mm/s, post-test velocity: 0.2 mm/s, maximum force: 50.0 N, trigger force: 0.005 N, load cell: 1 kg.

2.2.5 Magnetic resonance imaging (MRI)

MRI is commonly used in diagnostics of diseases in the human or animal body. ^{1}H NMR is applied to visualize mainly the distribution of water and mobile lipids in the tested system. The benchtop NMR can also be used to monitor water penetration, polymer swelling and the interaction of water molecules in tablets [18,19,70]. The interference of SE-based matrices with water could be shown and described the difference to other matrix formers.

The rotating charge of protons in the nucleus of the hydrogen atoms induces a magnetic dipole moment. Therefore the protons in the nucleus can be aligned with an external magnetic field. A transversal applied radiofrequency pulse deflects the protons out of the alignment to this field. The protons line up with the magnetic field again when the radiofrequency source is turned off. The time until protons are aligned again is the relaxation time of the protons. The relaxation time depends on the interaction of the hydrogen atoms with their environment (spin-lattice-relaxation T_1) [71]. The longest relaxation time occurs in free water with about 2.7 sec. The stronger the interaction with other substances the shorter the relaxation time will be. Depending on the relaxation time two zones can be determined in the T_2 graph (Figure 3). Over 1000 ms free water is detected and appears as dark parts in the T_1 weighted image because the signal is suppressed by a repetition of the image acquisition (n = 16 or 32 scans) with a short repetition time TR < T_1 to achieve better image contrast. Between 20 and 1000 ms interacting water can be detected and results in light parts, water with a relaxation time below 20 ms and therefore high interaction with the environment appears again as dark parts in the image. The intensity in the graph and therefore the intensity of the greyscales in the image stand for the amount of water in the indicated state. Decreasing amounts of free water and increasing amounts of interacting water can be observed during hydration of the sample. This amount can be calculated as the AUC in the indicated ranges and related to the dissolution time (see Annex Figure 3A). With this non-destructive method interactions between water and the tablet matrix can be visualized without any impact on the system by preparation prior to analysis.

A 20 MHz NMR benchtop system Maran DRX2 (Oxford Instruments, Abingdon, UK) capable of imaging was used for the MRI studies. Typical parameters for the used spin-echo-sequence were TE 9 ms, TR 150 or 300 ms, slice thickness 5 or 10 mm,

32 or 16 scans in 5 min. For some images a flow through cell was used. All images were T_1 weighted by the repetition time TR. The resolution was 64 x 64 data points for 20 x 20 mm field of view (FOV). The contrast is caused by the water concentration, T_1 and T_2 of the water protons in the tested three-dimensional region. For the T_2 experiment (Figure 3) the CPMG (Carr-Purcell-Meiboom-Gill) sequence was used. The 90° pulse length was fixed to 3.65 µs. The first echo was measured after 330 µs and increased in 270 µs steps. The relaxation delay was set 10 times higher as the longest component of the relaxation time distribution to avoid saturation effects on sample parts with very long relaxation times. 24 k data points and 16 averages were used as a general rule for a relaxation delay of 30 s.

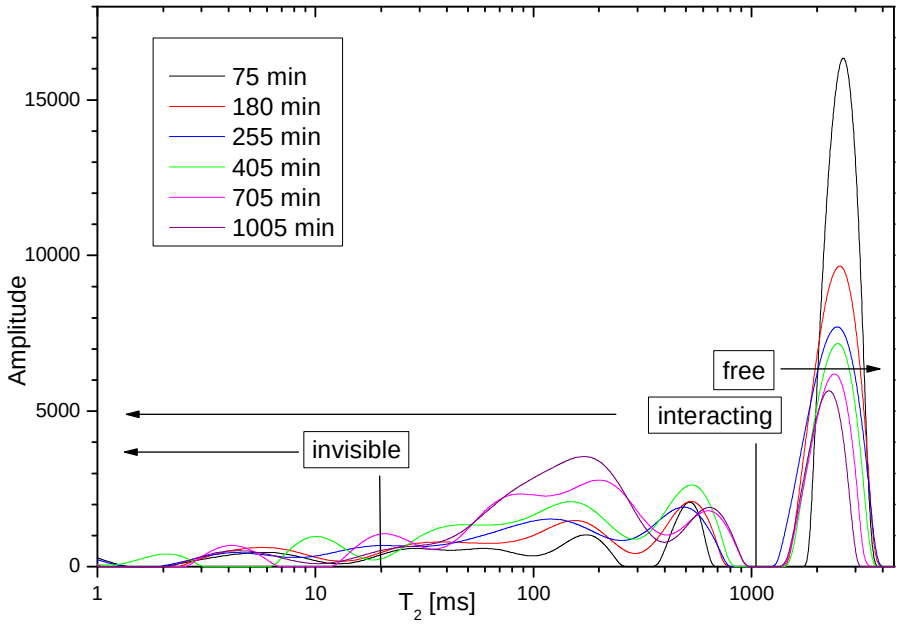


Figure 8. Relaxation curves of HPC tablets at different time points during hydration indicating the different states of water in the sample.

2.2.6 Light microscopy

The morphology of the granules, pellets and mini tablets was observed with an Olympus SZX12 Macroscope equipped with an Olympus ColorView video camera. The observation of the granules and pellets higher magnification of 7.4 and lower magnification of 1.5 was used. For the analysis of the texture analyser results, the

force standing for the detection of the dry tablet core has to be determined optically to use the data. The content of orange coloured riboflavin enabled the analysis of water penetration into the tablet by macroscopic observation. The vitamin visualized different zones in the tablet and gave more information on the matrix forming mechanism of different SEs (See chapter 5.1.4).

2.2.7 Digital picture analysis

Picture analysis was carried out using analySIS® 3.1, Soft Imaging System GmbH. The analysis of the different grey scales provides the opportunity to describe different zones in the tablets while water penetrates into the device. It is also possible to measure the size of the tablets and determine their swelling behavior.

2.2.8 Determination of water uptake and erosion behavior

Water uptake and erosion behavior studies were carried out in the dissolution vessel using the standard conditions for the dissolution studies (Chapter 2.2.2). After predetermined points in time samples were withdrawn from the with phosphate buffer pH 6.8 filled vessels and buffer solution remaining on the sample surface was removed using paper tissues. The samples were weighted and subsequently dried at 40 °C in a circulating air oven until mass constancy was achieved. The measurements were carried out in triplicate. The water uptake and erosion were calculated from the initial mean weight.

2.2.9 Camsizer analysis

For pellet and granule analysis a camsizer, Retsch GmbH, Haan, Germany was used to determine particle size distribution and shape characteristics of the pellets. The system is based on a two camera video analysis system taking 60 pictures per second of falling particles and determines different sizes of the particles such as Ferret diameter, Martin diameter, chord lengths and diameter of the coextensive circle. Using these parameters different shape characteristics can be calculated corresponding to the number of particles or the volume of the particles. In this case all calculations were analysed corresponding to the volume of the tested pellets.

Fe_{max} was analysed characterizing the maximum length of the pellet, c_{min} for the minimum diameter of the pellet. The area and circumference were calculated from the shadowed pixels of the particle. Volume, Length-Diameter ratio (L/D) and sphericity were calculated based on the formulas in Table 6. The perfect sphere would be described by a sphericity and L/D of 1. The number of measured particles lay between 8,000 and 150,000 particles per sample.

Table 6. Formula for calculation of shape characteristics of the particles.

Volume:	$V_{Ellipsoid} = \frac{\pi}{6} \cdot x_{Fe\max} \cdot x_c{}^2{}_{\min}$
Diameter-length ratio	$\frac{x_{c\,min}}{x_{Fe\,max}}$
Sphericity	$\frac{4\pi A}{U^2}$

2.2.10 Thermal polarised light microscopy

Studies on the thermal behavior and melting characteristics of SEs S-370, S-570, S-770, S-1170 and S-1670 were carried out in the dry state by thermal polarised light microscopy using a Leitz Laborlux 12 POL, Wetzlar, Germany equipped with a heated sample table Mettler FP5 and a FP52 central processor. Magnification: x 100. Heating rate: 15 °C/min. Pictures were taken using a JVC TKC1380E video camera, JVC Ltd., Japan. Phase transitions and the clearing point were determined optically.

2.2.11 Theoretical methods

The following analytical solutions of Fick's second law of diffusion considering the given initial and boundary conditions were used to quantitatively describe the experimentally determined vitamin release kinetics from the obtained granules, pellets and tablets. In the case of granules and most pellets the sphere was assumed to be the predominant geometrical form where vitamin release can be described by the following equation [72]:

$$\frac{M_\infty - M_t}{M_\infty} = \frac{6}{\Pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{n^2} \cdot \exp\left(- \frac{n^2 \cdot \pi^2}{R^2} \cdot D \cdot t \right)$$

Equation 1. Solution of Fick's second law under consideration of the sphere geometry.

The vitamin release from the cylindrical matrices was described in the calculations for the mini tablets and pellets (in case of the release from pellets of different length), taking into account radial as well as axial mass transfer. Based on these calculations the diffusion coefficients for every vitamin could be determined by the following solution [17]:

$$\frac{M_t}{M_\infty} = 1 - \frac{32}{\pi^2} \cdot \sum_{n=1}^{\infty} \frac{1}{q_n^2} \cdot \exp\left(- \frac{q_n^2}{R_c^2} \cdot D \cdot t \right) \cdot \sum_{p=0}^{\infty} \frac{1}{(2 \cdot p + 1)^2} \cdot \exp\left(- \frac{(2 \cdot p + 1)^2 \cdot \pi^2}{H_c^2} \cdot D \cdot t \right)$$

Equation 2. Solution of Fick's second law under consideration of the cylindrical geometry.

In both equations M_∞ and M_t denote the absolute cumulative amounts of vitamin released at infinite time and time t, respectively. R represents the radius of the granules and D the apparent diffusion coefficient of the vitamin within the system. The geometrical form of the tablets is described by the radius R_c and height H_c. q_n are the roots of the Bessel function of the first kind of order zero [$J_0(q_n) = 0$]. For perfect application of the formulas the initial and boundary conditions have to be the following:

(i) homogenously dispersed ingredients in the dosage form,

(ii) molecularly dispersed ingredients in the matrix,

(iii) sink conditions throughout the experiment,

(iv) constant mass transfer coefficient through the dosage form.

Whenever these conditions are not fully given deviations of the experimental curves and the fitted curves can occur. In all cases a good fit must not mean that diffusion is

the only predominant mass transport mechanism. Overlays of other effects can influence the release pattern and simulate a diffusion controlled release. To make sure that the mass transport mechanism determined is right, other characteristics of the formulation have to be known.

2.2.12 Preparation of granules

Granules containing nicotinamide, pyridoxine, thiamine and riboflavin were prepared by

(i) melt granulation

(ii) wet granulation

(iii) compression & grinding.

SEs, lipids and hydrogels were used as matrix formers. The composition of the granules varied as indicated. All compounds were mixed in a tumble blender (Turbula, W.A. Bachofen AG, Muttenz, Switzerland) for 30 min. In the case of melt granulation the blend was heated to 80 °C (water bath) and manually mixed in a mortar. Afterwards, the granules were cooled down to room temperature. In the case of wet granulation the blend was intensively mixed with purified water in a bowl and dried on a sheet at room temperature over night. In the case of compaction the blend was compressed into tablets using an eccentric tableting machine (Fette E1, Schwarzenbek, Germany). All granules were granulated over a 4 mm granulation sieve (Turbo sieve, L.B.Bohle, Ennigerloh, Germany) and afterwards classified into the indicated fraction by sieving (0.5 mm, 1.0 mm, 1.6 mm and 2.0 mm, Retsch GmbH, Haan, Germany). Depending on the concentration of the vitamins in the matrix 150 - 500 mg granules contained one daily dose of the vitamins. All indications of content in the compositions are displayed in percent by weight (w/w).

2.2.13 Preparation of mini tablets

Mini tablets were produced using the 0.5 - 1.0 mm fraction of the previously manufactured granules. This fraction of the granules was compressed into tablets with a diameter of 5 mm using an eccentric tablet machine (Fette E1, Schwarzenbek, Germany). The tablets were manufactured without any further additives. Depending

on the concentration of the vitamins in the matrix 3 - 9 tablets contained one daily dose of the vitamins. All indications of content in the compositions are displayed in percent by weight (w/w).

2.2.14 Preparation of pellets

Extrusion/spheronization studies were carried out using a twin screw extruder DE-40-T, Gabler GmbH & Co. KG, Ettlingen, Germany with melt extrusion capability. The spheronizer used was a R-250, Gabler GmbH & Co. KG, Ettlingen, Germany. Extrusion and spheronization parameters were adjusted to the different formulations as indicated in the studies. Prior to spheronization the extruded strands were broken manually or milled into shorter pieces using the methods indicated in the studies. 500 mg pellets contained one daily dose of the vitamins in all cases. All indications of content in the compositions are displayed in percent by weight (w/w).

2.2.15 Preparation of tablets

The ingredients were mixed in a tumble blender for 30 min and subsequently compressed by direct compression on an eccentric tablet machine (Fette E1, Schwarzenbek, Germany) with the indicated tablet tools. When indicated, the tablets were tempered at 30 or 40 ℃ in a Heraeus vacutherm VT 6130M drying oven, Kendro Laboratory products, Hanau, Germany over the indicated period of time. All indications of content in the compositions are displayed in percent by weight (w/w).

2.2.16 Preparation of three layer tablets

Three-layer tablets were produced using a Elizabeth HATA AP45-LSU-3L three-layer tablet machine, North Huntington, PA, USA or a Fette 102i with capability for three-layer compression (Fette GmbH, Schwarzenbek, Germany). Three-layer tablets were produced using direct compression. Mixtures were obtained using a container or tumble blender. Blending time was individually adjusted to each tableting mixture. All indications of content in the compositions are displayed in percent by weight (w/w).

2.2.17 Storage conditions

Stability studies were carried out in controlled walk-in climate chambers at the indicated conditions. For the granule and mini tablet stability studies the dosage forms were stored in PP containers and in CSP active vials at 25 °C/60 % r.h.. The stability of the pellets were monitored in PP containers at 25 °C/60 % r.h., 30 °C/65 % r.h. and 40 °C/75 % r.h..

3 Characterization of different sucrose ester types

3.1 Experimental results and discussion

3.1.1 Thermal polarised light microscopy

The description of the first liquid crystal was published in 1888. F. Reinitzer described colourful changes when cholesteryl benzoate was molten and cooled down again. He observed that the substance became liquid at 145 °C but the milky look and polarised microscopic double breakage still occurred until 175 °C. O. Lehmann did further research on the topic and was the first who talked about “liquid crystals” [73]. In 1911 E. Fischer first reported the existence of liquid crystalline behavior in long-chain n-alkyl pyranosides [74]. It is known that also other amphiphilic carbohydrates can form liquid crystalline mesophases when exposed to heat [26,75-81]. The transition from solid to liquid state is not straightforward in liquid crystals. They form different mesophases such as different smectic phases or a nematic phase before they pass into the isotropic liquid. In amphiphilic structures the same intramolecular contradiction exists as in technical liquid crystals used for LC displays which leads to the formation of the mesophases. H-bonds and van der Waals linkages connect the molecular parts with each other. The hydrophilic and lipophilic parts of the molecule represent the momentum of the self-organisation in the liquid crystalline state. Therefore the HLB number of the substance is important for the formation of the mesophases. Consequently, the SEs used should also appear in this group and form thermotropic liquid crystals. Thermic polarised light microscopy was carried out to describe the thermic behavior of the SEs used. The aim of the investigation was to find out at which point the liquid crystalline phases change and when the clearing point and therefore the isotropic liquid is reached. Astonishingly, the isotropic liquid was not reached within the given melting ranges indicated by the manufacturer. All

tested SE mixtures (SE S-370, S-570, S-770, S-1170 and S-1670) still showed liquid crystalline phase behavior up to 80 °C as well as double breakage of the polarised light. The formation of organized structures in the liquid crystals could be observed (Figure 4). Several publications identified smectic A* (lamellar), cubic and columnar phases in pure SEs [24,27]. The SEs used in this study are blends of different SE molecules which is why the mesophases are very difficult to characterize. Figure 4 shows images of the SEs at different temperatures. Characteristic formations of carbohydrate liquid crystals can be observed. For example, SE S-770 shows typical fan-like (columnar) and lamellar (smectic) structures at 150 °C.

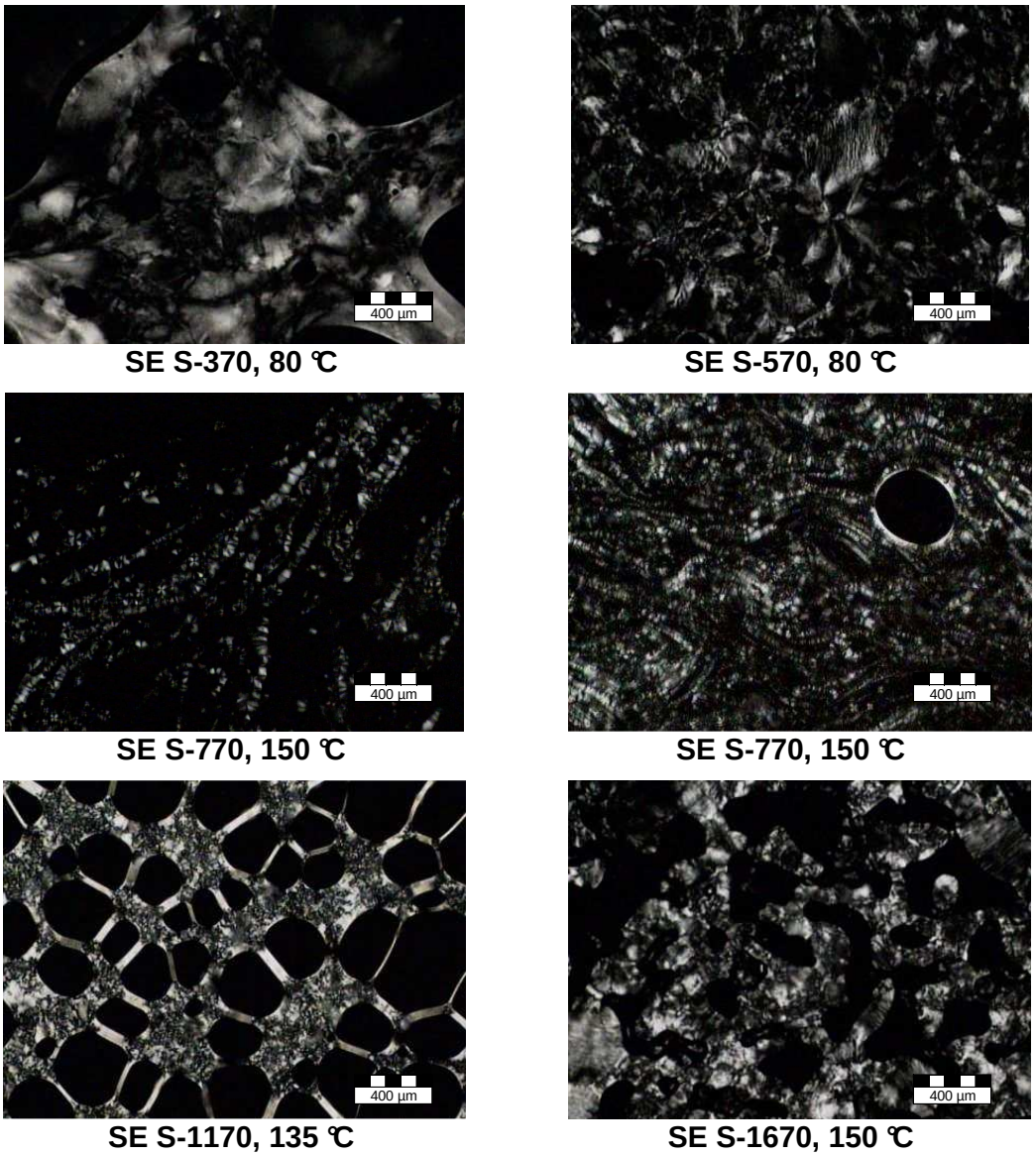


Figure 10. Photographs of different SEs under thermal polarised light microscope at the indicated temperatures.

The clearing point of the SEs could be determined optically using POM (Table 7). Therefore all SEs will be in liquid crystalline mesophases when melt granulation or extrusion processes are carried out at 50 - 80 ℃.

Table 7. Melting range and clearing point of SE mixtures used.

SE type	**Melting range** indicated by the supplier	**Clearing point** (in brackets: clearing point without shear strain)
SE S-370	51 - 69 ℃	~ 85 ℃
SE S-570	50 - 65 ℃	~ 130 ℃
SE S-770	49 - 60 ℃	~ 135 - 150 ℃ (180 ℃)
SE S-1170	49 - 55 ℃	~ 167 ℃ (>180 ℃)
SE S-1670	49 - 56 ℃	> 180 ℃

An increasing HLB value resulted in higher stability of the mesophase. The stability of the mesophase is indicated by a high temperature of the clearing point. The sterical form of the esters may be a potential cause for this. SE mixtures with high HLB values contain mainly mono- and diesters which can stabilize the formation of the mesophases. SEs with low HLB values also contain tri- to pentaesters which may destabilize the liquid crystalline structure. This is caused by the higher number of fatty acids esterified to the sugar molecule which hinders a strong linkage of the sugar to the other sugar molecules and no formation of systematic structures may arise. It was also reported that the “melts” of SEs with high HLB values do not flow [21]. The reason for this may be that the liquid crystalline mesophase is very stable and therefore high viscosity in the liquid crystals occurs.

Shear induced phase transitions have been reported before by Molinier [28]. In addition, this study showed that the heating rate can change the phase transition temperature of the more stable mesophases of SEs S-770 and S-1170. The clearing point could be determined when manual force was put onto the samples. However, without mechanic influence no isotropic state could be determined. SE S-1170 shows the formation of “oily streaks” which can occur in chiral smectic phases, also called

cholesteric phases (Figure 5) [82-84]. At a temperature of > 130 ℃ already a smell of caramelised sugar was observed indicating the beginning of decomposition of the material. All of these findings are essential for the development of an extrusion or melt granulation process. SE strands will always have a milky look because of liquid crystalline formation and will not get the clear look of stands formed from polymers which show glass transition and which are therefore in the amorphous state.

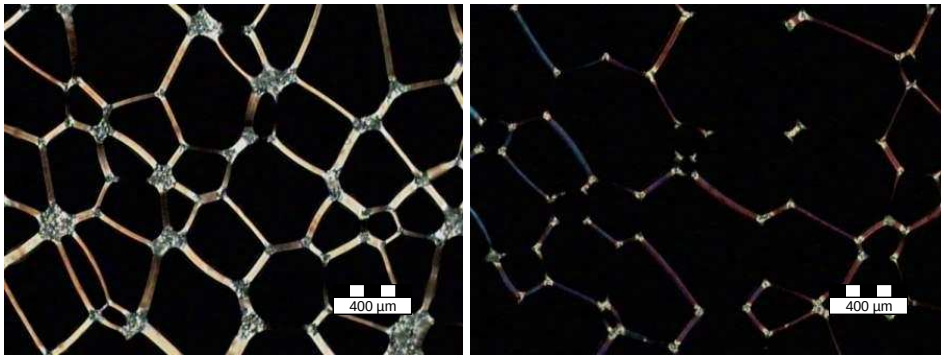


Figure 12. SE S-1170 at 133 - 143℃ without shear strain, showing the structure of "oily streaks".

3.1.1 DSC studies

Differential scanning calorimetry is a well-known method to characterize substances in their thermal behavior. At a constant heating rate a constant amount of energy is brought into the sample. Glass transition, melting points, amorph and crystalline states can be determined by scanning the kinetic energy of the substances over a broad range of thermal changing. Usually, the glass transition temperature has to be determined in order to set extrusion parameters for the melt extrusion process. The thermograms of SEs do not show glass transition although they form a kind of "glassy state" when they are heated and cooled down again. This observation lead to the theory that the glass transition might be covered by the broad phase transition peaks of the different substances in the SE powder. A baseline shift suggests this. Szuts reported a baseline shift in the thermogram of the SEs and postulated a covered glass transition [21]. The samples in this study also show a slight shift (Figure 6).

For substances with liquid crystalline behavior also small energy changes as needed for liquid crystalline phase transition can be detected by DSC and later optically characterized through thermal polarised light microscopy. In the case of SEs it is

difficult to describe the processes under thermal treatment. The manufacturer indicate the peaks in the DSC thermogram as the melting temperatures. However, following the melting process under polarised light, research showed that not an isotropic melt is reached at these points but a liquid crystalline phase as it is described for similar structures in other publications [85]. The DSC thermograms still provide a lot of information about phase transition temperatures and recrystallisation behavior which can be useful for knowing sucrose fatty acid esters much better.

When working with melting technologies the melting characteristics of all ingredients should be known. The melting points of all used vitamins lay over the applied temperatures in manufacturing of 50 - 80 °C. All "melting ranges" of SEs were approved (see thermogram in Annex Figure 4A). Figure 6 shows the heating curves of SE S-370, S-770 and S-1170 with a heating rate of 10 K/min to 80 °C (S-370) or 90 °C (S-770 and S-1170) as well as the reheating curves directly after cooling. SE S-770 and S-1170 were heated to 90 °C where they are still in the liquid crystalline state. SE S-370 could only be heated to 80 °C because the substance reaches the isotropic liquid as early as 85 °C (Table 7).

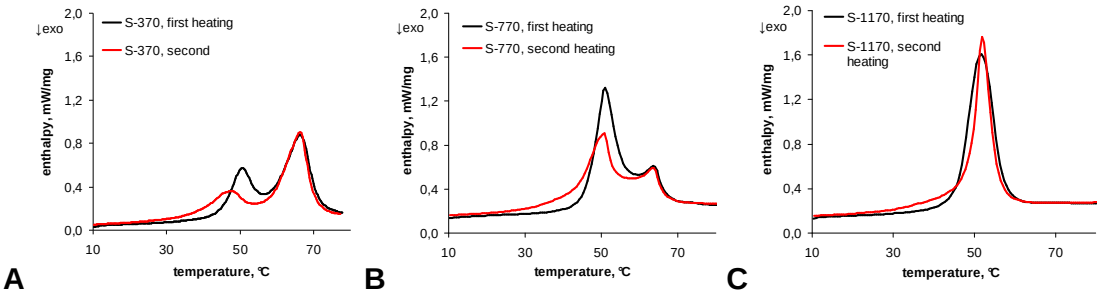


Figure 13. DSC thermogram of SEs S-370 (A), S-770 (B) and S-1170 (C) with double heating (black curve: first heating, red curve: second heating), heating rate: 10 K/min from 10 °C to 80 °C/ 90 °C, cooling, reheating.

The phase transition peaks look very similar in first and second heating, only slight changes in the AUC can be detected. This indicates a quick recrystallisation of the material when the SEs are only heated to the liquid crystalline state but not reached the isotropic liquid. The mobility of the molecules is not very high in the liquid crystalline state, that they cannot change their organization in the structure which leads to similar formation of the crystals as seen in the first heating.

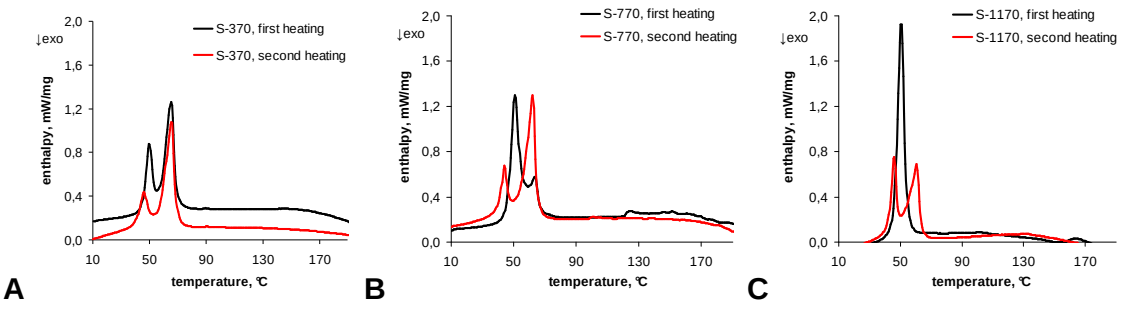


Figure 14. DSC thermogram of SE S-370 (A), S-770 (B) and S-1170 with double heating (black curve: first heating, grey curve: second heating), heating rate: 10 K/min from 10 ℃ to 190 ℃, cooling, reheating. Thermograms of SE S-370, S-770 and S-1170 at different heating programms are shown in Annex Figures 5A - 7A.

In Figure 7 the situation is very different. When the SEs are heated to high temperatures and the mobility of the molecules is higher, the organisation in the different liquid crystalline states can change. When the material is cooled down again, the time is too short for complete recrystallization. Other polymorphous states or molecular formations still exist, leading to different energy profiles which are needed to convert the SE back into the liquid crystalline state. Szuts reported a recrystallization time for SE S-370 of 1 - 4 weeks. SE S-1670 was not completely recrystallized after 4 weeks [21] after it has been heated to 100 ℃. The same tendencies are found in this DSC study. SE S-370 showed only slight changes of the energy profile in the first peak which indicates the fastest recrystallisation in this type. The changes in SE S-770 and S-1170 are much greater. The enthalpy of the peaks in SE S-770 is vice versa in the second heating. In SE S-1170 even two peaks appear in the second heating where one peak has been in the first heating. For the development of pharmaceutical preparations it should be taken into account, that the manufacturing temperature has an influence on the recrystallisation time which itself can have an impact on the release profile or the stability of the product. It should be investigated if there is any influence on the performance of the product.

3.2 Conclusion of the characterization studies

After the analysis of the DSC and POM studies it can be proven that also the used SE types form thermotropic liquid crystalline mesophases. In melting technologies this fact has to be considered when developing new formulations. Within the applied manufacturing temperatures the SEs will always be in the liquid crystalline state. SE S-370 is the only SE which can reach the isotropic liquid under 100 °C. After the transition into the liquid crystalline phases the SE can be formed and keep their shape after cooling down to room temperature. They form an opalescent glassy state which has not an amorph order of the molecules. The order of the molecules after phase transition and cooling should be investigated further. The tendency that the viscosity increases in higher HLB values should be proved and measured to evaluate the use of all SE in extrusion technology. The manufacturing temperature is important for the stability of the product. When SEs are heated to the isotropic liquid during manufacturing the recrystallization time of the SE used has to be known to produce a save and stable product. When SEs are only heated to their liquid crystalline state the recrystallization time is expected to be within the production time of the product. The reproducibility of the product performance and the stability over storage time should be proven (see investigations on storage stability). The use of liquid crystals is not widely described for pharmaceutical use. More investigation should be carried out to benefit the advantages of liquid crystalline phase behavior in solid dosage forms. The functionality could be used for different applications and hold the chance to formulated difficult drug substances. The investigations in technical application of liquid crystals can give a lot of information for further investigation.

4 Sucrose ester-based granules

Multi-particulate systems offer a wide range of applications and therefore are very interesting dosage forms. Granules can be used as fillings for capsules, can be compressed into tablets or packed in sachets. The bioavailability of drugs released from multi-particulate systems show better reproducibility than from monolithic dosage forms and the danger of dose dumping is lowered. Multi-particulate systems with sustained release patterns are often produced as pellet or granule formulations coated with functional films which determine the release profiles. This technique includes an additional manufacturing step compared to matrix formulations, which enhances production costs for the product. Materials which enable matrix formulations for multi-particulate systems are needed to lower production costs and offer an additional way to formulate even good soluble drugs in sustained release granule formulations. Lipid matrices are often used to formulate preparations containing good soluble substances. SEs cover the whole HLB value range, which could, depending on the characteristics of the incorporated drug, make it possible to alter the hydrophilicity of the matrix in order to achieve the desired release profile for each substance.

The first studies investigate whether SEs are able to sustain the release of well-soluble vitamins at all. The aim was to determine, if and over which period of time SEs can sustain the release of different vitamins from multi-particulate formulations. The release mechanism of active ingredients with different physico-chemical properties from SE-based formulations have not been reported in the literature. This chapter discusses the influence of type and concentration of SE in the matrix, different manufacturing methods and properties of the active ingredients on the release mechanism. Nicotinamide, pyridoxine, riboflavin and thiamine were chosen as active ingredients due to their different water solubility, molecular structure and molecular weight. Depending on the concentration of vitamins in the matrix 150 to 500 mg of granules contained one daily dose of the vitamins which is 18 mg for nicotinamide, 2 mg for pyridoxine, 1.6 mg for riboflavin and 1.4 mg for thiamine [42].

Mathematical solutions can be used to determine the release kinetics from different drug delivery systems (DDS) by curve fitting. Due to the wide range of DDS there are

different mathematical models describing the drug release from the different systems. The formula which fits best to the system used has to be chosen. Many phenomena which influence the drug release from a dosage form must be taken into account. Additionally, changes in the device geometry, water penetration into the device, drug and excipient dissolution, creation of water filled pores or physical drug-excipient interaction [17,86-91] can occur. Mechanistic realistic mathematical models are always based on equations which describe real phenomena e.g. diffusion, dissolution of particles or phase transition of polymers. In this study a solution of Fick's second law was used to describe the release kinetics from the system. As a result, diffusion was assumed to be the predominating mass transport mechanism in the system. The initial and boundary conditions given throughout the experiment were taken into consideration when choosing this solution. If the postulate of diffusion being the predominating mass transport mechanism is right, the experimental results should perfectly match the calculated curve.

4.1 Experimental results and discussion

4.1.1 Granule morphology and hardness

Figure 8 shows photomicrographs of vitamin-loaded, SE S-370-based granules prepared using (A) melt granulation, (B) wet granulation or (C) compression & grinding. The upper row shows ensembles of granules at lower magnification, the lower row single granules at higher magnification. The systems consist of 3.6 % nicotinamide, 0.5 % pyridoxine hydrochloride, 0.4 % thiamine nitrate, 0.3 % riboflavin (5 % vitamins in total), 80 % SE and 15 % MCC. The images show that in all cases similarly shaped particles were obtained, with a relatively narrow size distribution in the sieve fraction. The geometry of the granules might best be approximated by that of a sphere or ellipsoid. The yellow color is incurred by riboflavin (all other compounds are colorless or white). Importantly, the uniformity of the color indicates that riboflavin is homogeneously distributed throughout the systems. The differences in the brightness of the color can probably be explained as follows: During melt granulation riboflavin can be expected to (at least partially) dissolve in the molten SE and might (at least partially) remain in this state upon cooling. During wet granulation riboflavin first dissolves in the granulation fluid (purified water) and then re-precipitates upon drying. This can be expected to result in a finer riboflavin particle

distribution compared to that in granules prepared by compression & grinding. During the latter preparation technique, the vitamin remains in the solid state. At the end of the release experiments, all granules were white, indicating that riboflavin was completely released. The hardness of the granules produced decreased in the following ranking order: melt granulation (3.02 ± 0.76 N) > compression & grinding (1.15 ± 0.13 N) > wet granulation (0.76 ± 0.315 N). These differences can be attributed to the type and strength of bonds created during granulation between the SE and vitamin particles. Granules prepared by melt granulation or compression & grinding were sufficiently stable to remain intact throughout the vitamin release experiments. In contrast, granules prepared by wet granulation rapidly disintegrated upon exposure to the release medium.

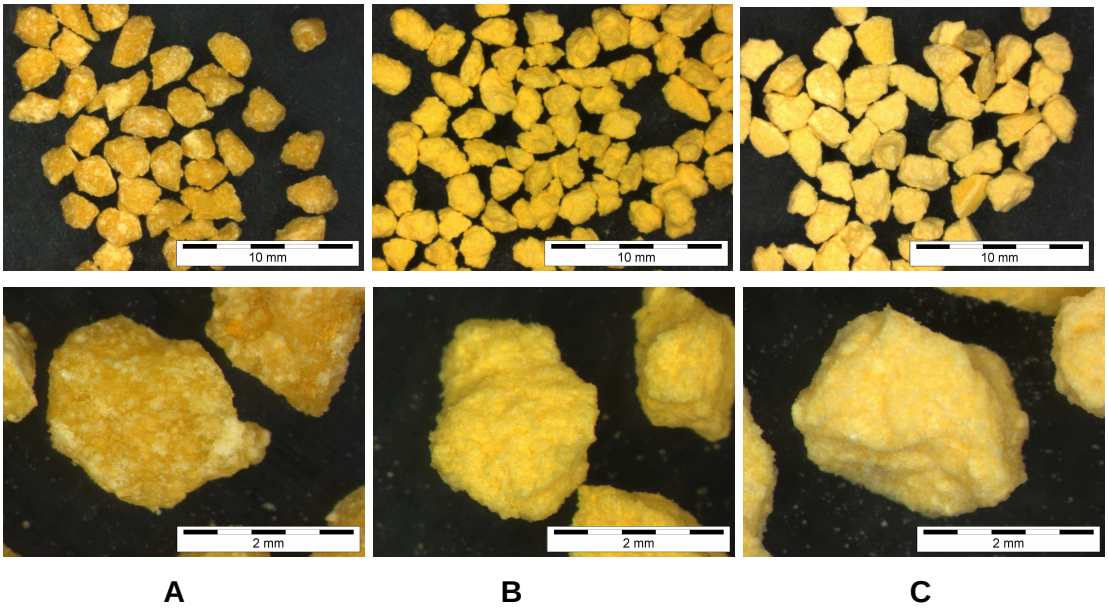


Figure 15. Optical microscopy pictures of granules prepared by (A) melt granulation, (B) wet granulation, and (C) compression & grinding (SE S-370; SE content: 80 %).

4.1.2 Simultaneous vitamin release

The symbols in Figure 9 show the experimentally determined vitamin release kinetics from granules prepared by: (A) melt granulation and (B) compression & grinding. The systems consisted of 5 % vitamins, 80 % SE S-370 and 15 % MCC (sieve fraction: 1.0 - 1.6 mm). The release of the vitamins exhibiting very different aqueous solubility could be effectively and simultaneously controlled in the case of melt granulation and compression & grinding.

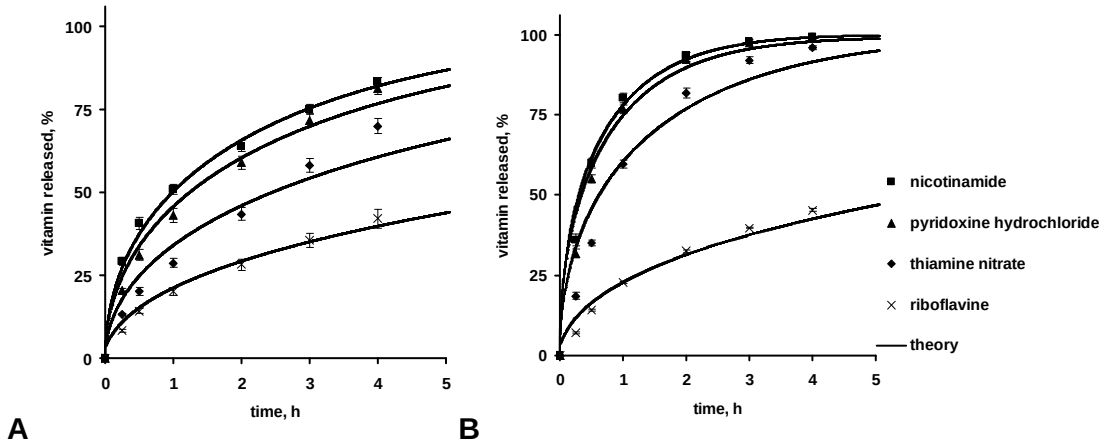


Figure 16. Simultaneous controlled vitamin release from granules based on SE S-370 into phosphate buffer pH 6.8. Granule preparation technique: (A) melt granulation, (B) compression & grinding (SE content: 80 %; sieve fraction: 1.0 - 1.6 mm) (symbols: experimental results, curves: theory).

In contrast, in the case of wet granulation the release of the “lower” molecular weight vitamins was rapid and only the release of riboflavin (376.37 Da) was sustained (For release curves see Annex Figure 8A). This can at least partially be attributed to the lower mechanical stability of the granules indicating that the strength of the inter-particle bonds created during wet granulation is much lower than in the two other cases. Thus, less hindrance for water and vitamin transport can be expected in these systems. The fact that only riboflavin release was sustained from granules prepared by wet granulation is probably due to its higher molecular weight (376.37 Da versus 122.13 Da, 170.18 Da and 265.35 Da for nicotinamide, pyridoxine H^+ and thiamine cations; note that the ionized species is likely to diffuse, not the salt). Due to the rapid release of most vitamins from granules prepared by wet granulation, this type of delivery system was not studied in any further detail. No calculation of the diffusion coefficients was carried out for these granules because of erosion occurring in the wet granules. The predominant conditions do not longer meet the initial and boundary conditions for the application of Fick’s second law.

Interestingly, the rate of vitamin release generally decreased in the following ranking order: nicotinamide > pyridoxine hydrochloride > thiamine nitrate > riboflavin, irrespective of the type of preparation technique of the granules (Figure 9). This

ranking order corresponds well to the: (i) decrease in aqueous solubility, as well as to the (ii) increase in molecular weight of the vitamins/vitamin ions.

In order to get deeper insight into the underlying mass transport phenomena, which are of major importance for the control of vitamin release from these granules, Fick's second law of diffusion was used to quantify the observed nicotinamide, pyridoxine hydrochloride, thiamine nitrate and riboflavin release kinetics. The curves in Figure 9 show the fittings of this theory (Equation 1) to the experimentally determined vitamin release kinetics from the different types of granules. Clearly, good agreement between theory and experiment was obtained in most cases, indicating that it likely that diffusion is the release rate controlling mass transport step; irrespective of the type of preparation method (except for wet granulation) and type of vitamin. For thiamine nitrate the highest deviation between experimental results and the fitted curve occurred in both granules. In the beginning the release is slower as expected and in the end the release is faster as expected. Thiamine is the only vitamin in the tested range with permanent positive charge within the molecule which can have an effect on the release when ionic structures are present. In SEs this is not the case and is not likely to influence the release patterns. Even if a good fit can be achieved it does not mean that diffusion is the controlling mass transport mechanism. The diffusion coefficient can be overlaid by dissolution effects of the substance particles or the effect of diffusion of water into the system. If there is not effect of the matrix onto the release of the substance the diffusion of water into the system can pretend a release controlled by the diffusion of the substance. To verify, if diffusion the predominant mass transport mechanism in the case of thiamine nitrate more experimental results are needed. This case will be discussed later when more formulations are tested and more information of the release behavior is available. Based on the calculations, the following apparent diffusion coefficients of the vitamins in the granules could be determined, postulating that thiamine nitrate is also diffusion controlled: (i) melt granulation: D (nicotinamide) = 3.7 (± 0.2) 10^{-8}cm^2/s, D (pyridoxine hydrochloride) = 2.9 (± 0.3) 10^{-8}cm^2/s, D (thiamine cation in the case of thiamine nitrate) = 1.5 (± 0.1) 10^{-8}cm^2/s, D (riboflavin) = 0.5 (± 0.1) 10^{-8}cm^2/s, and (ii) compression & grinding: D (nicotinamide) = 12.3 (± 0.9) 10^{-8}cm^2/s, D (pyridoxine hydrochloride) = 11.0 (± 0.3) 10^{-8}cm^2/s, D (thiamine cation in the case of thiamine nitrate) = 5.8 (± 0.4) 10^{-8}cm^2/s, D (riboflavin) = 0.6 (± 0.01) 10^{-8}cm^2/s.

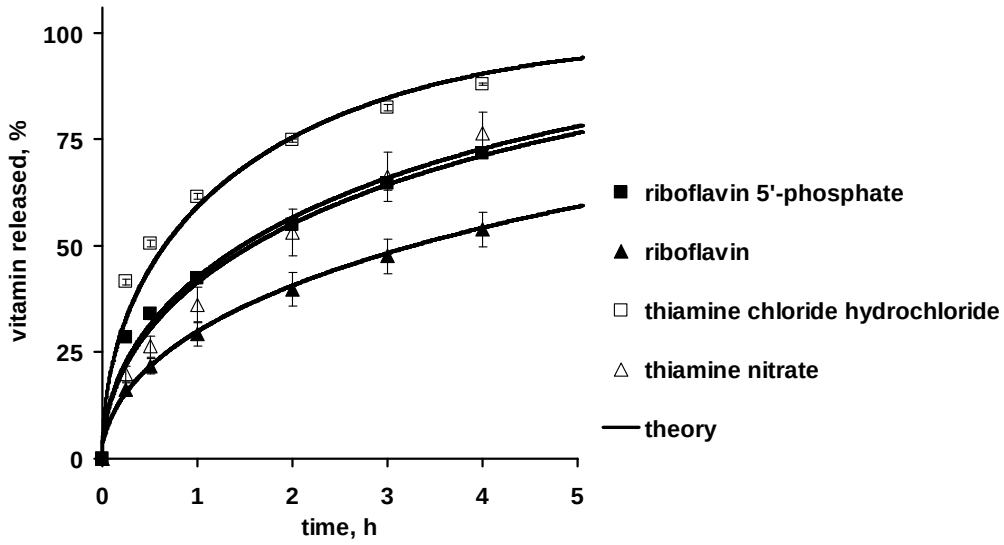


Figure 17. Vitamin release from granules containing thiamine chloride and riboflavin-5'-phosphate, and from granules containing thiamine nitrate and riboflavin in phosphate buffer pH 6.8 (melt granulation; SE S-370; sieve fraction: 1.0-1.6 mm, granules also contained nicotinamide and pyridoxine hydrochloride).

As it can be seen, these values show that the mobility of the vitamins within the granules is strongly affected by their molecular weight but also the water solubility can have an effect on the release kinetics. In order to know, whether one of these two aspects dominates the release from SE S-370-based granules containing thiamine chloride instead of thiamine nitrate and riboflavin 5'-phosphate instead of riboflavin were prepared by melt granulation. The solubility of these compounds is very much increased (1000 versus 27 g/L and 112 versus 0.07 g/L, respectively), whereas the molecular weight of the diffusing species is unaltered in the case of thiamine (same cation) and increased in the case of riboflavin 5'-phosphate. The dissolution studies and the curve fitting from the formulation containing 80 % SE S-370, 15 % MCC and 5 % total vitamins were determined (Figure 10). Nicotinamide and pyridoxine hydrochloride were also contained in the formulation and showed constant diffusion coefficients from the formulations containing the different thiamine and riboflavin salts. It can be observed that the release of the better soluble salts is much faster what confirms that not only the molecular weight is a predominating factor for the release of vitamins from sucrose ester-based granules. The diffusion coefficients rise from D (thiamine cation in the case of thiamine nitrate) = 2.3

(± 0.5) 10^{-8}cm^2/s to D (thiamine cation in the case of thiamine chloride hydrochloride) = 5.5 (± 0.2) 10^{-8}cm^2/s and from D (riboflavin) = 1.1 (± 0.2) 10^{-8}cm^2/s to D (riboflavin 5'-phosphate) = 2.5 (± 0.2) 10^{-8} cm^2/s. The ranking order of the vitamins although is unchanged in this study. The diffusion coefficient of thiamine chloride hydrochloride reaches the same level as for pyridoxine hydrochloride. This study shows that not only the molecular weight but also the water solubility of the substances has an impact on the release patterns. The main effect of water solubility seems to be within the first 15 min. Fast dissolution of the vitamin leads to high dissolved amount after 15 min. The release rates and therefore the curves are afterwards nearly parallel.

4.1.3 Importance of the granule size

The formulation containing 80 % of SE S-370 was analyzed for the influence of the sieve fraction of the granules on the release profile. The granules obtained by melt granulation and compression & grinding have been chosen to determine this effect between sieve fraction 1.0 - 1.6 mm and 0.5 - 1.0 mm. Considering the results of the first study the difference in length of the diffusion pathways should occur in faster release of the vitamins. The diameter of the particles is part of the equation and is calculated into the coefficients for both granules therefore the diffusion coefficients should maintain when only the increase of the diffusion pathway is the reason for the increased release rate. The predicted release curves were calculated for the sieve fraction 0.5 - 1.0 mm (Figure 11) depending on the known diffusion coefficient in the sieve fraction 1.0 - 1.6 mm. The predicted release curves fit to the experimental results of the granules. In the case of 1.0 - 1.6 mm granules the expected release is slightly slower than the experimental results. In the case of the smaller granules the results are vice versa. Especially in the case of granules the geometrical form of the particles leads to higher deviations between modeling and experiments. In the formula a spherical form of the particles is assumed, but the granules show an angular shape. But taking this knowledge into account, again the ranking order of the release rates follows the ranking of the molecular weight. The release rates of all vitamins increase from the sieve fraction 1.0 - 1.6 mm to 0.5 - 1.0 mm as expected. The tendency showing that the release is controlled predominantly by diffusion and the mobility of the species is mainly determined by their molecular weight can be seen again in this study.

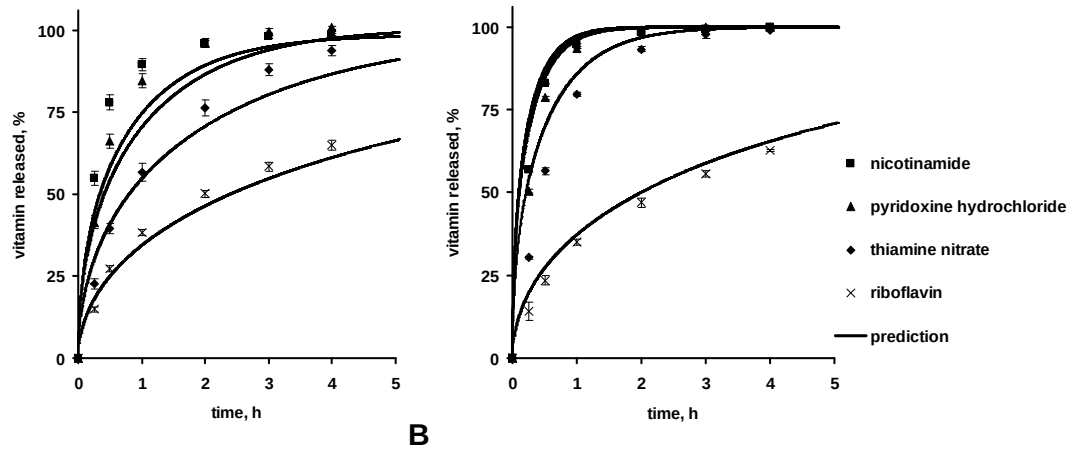


Figure 18. Predicted curves for sieve fraction 0.5 - 1.0 mm from sieve fraction 1.0-1.6 mm in phosphate buffer pH 6.8 from systems prepared by: (A) melt granulation, or (B) compression & grinding (80 % SE S-370) (symbols: experimental results, curves: prediction).

4.1.4 Effects of the type of matrix former

In the first studies only SE S-370 was investigated. The focus of the following study was to investigate the influence of different matrix formers on the release behavior of the chosen vitamins. Two Glycerol esters, Glycerol dipalmitostearate and Glycerol behenate, were compared to the lipophilic SE S-370 (HLB 3) and the amphiphilic SE S-1170 (HLB 11) (Figure 12). Formulations containing 50 % of matrix forming agent were chosen to produce granules by melt granulation and determine the simultaneous release of the different vitamins. Ethylcellulose was used as a filling agent. In all formulations a big difference in the release rate of the three good water soluble vitamins and riboflavin was observed.

All formulations were able to sustain the release of riboflavin, showing the lowest water solubility and the highest molecular weight among the tested vitamins and therefore the lowest mobility of the molecule in the matrix. The retardation effect of Glycerol dipalmitostearate, Glycerol behenate and the lipophilic SE S-370 on the release of nicotinamide, pyridoxine hydrochloride or thiamine nitrate decreased again the ranking order of the molecular weight. 50 - 60 % of riboflavin was released after 1 h whereas the other vitamins showed 70 - 100 % release. The hydrophilic SE S-1170 (Figure 12, B) did not sustain the release of the small vitamins at all.

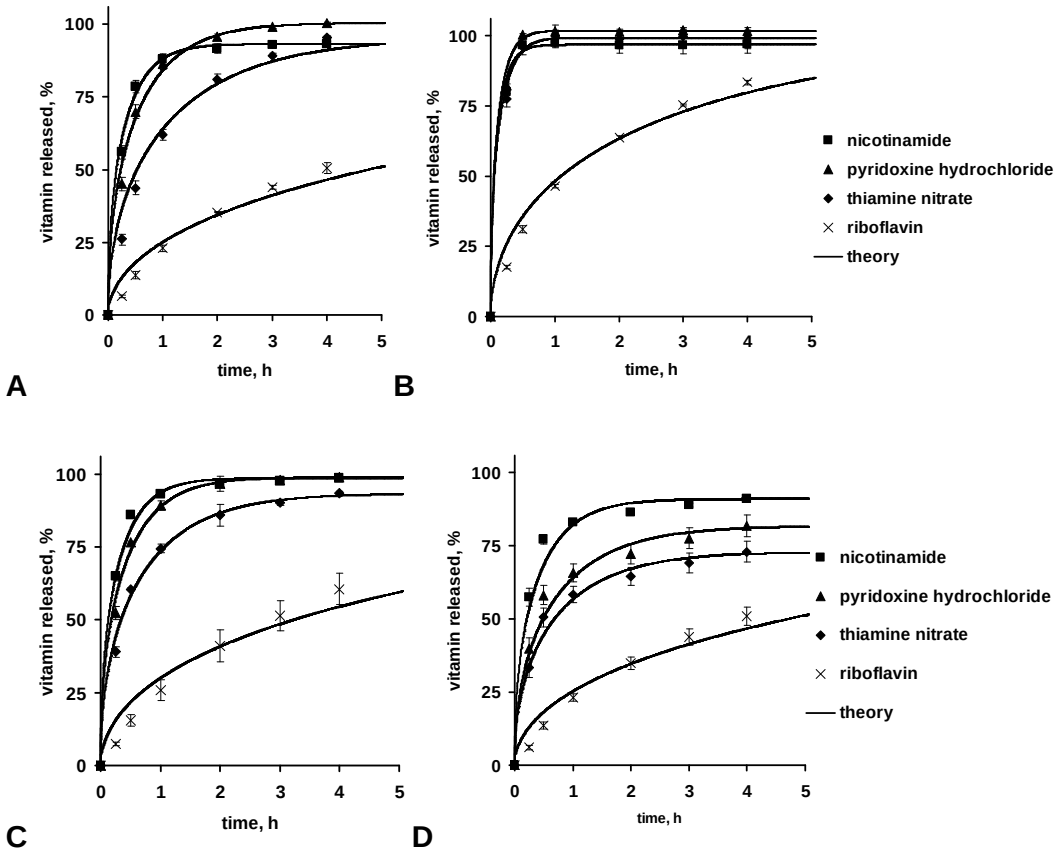


Figure 19. Effects of the type of matrix former on simultaneous vitamin release from granules in phosphate buffer pH 6.8: (A) SE S-370, (B) SE S-1170, (C) glyceryl behenate, (D) glyceryl dipalmitostearate (matrix former content: 50 %; sieve fraction: 0.5 - 1.0 mm; melt granulation) (symbols: experimental results, curves: theory).

The release of these vitamins was completed after 30 minutes. However, riboflavin can be sustained over more than 4 h in this amphiphilic matrix. The diffusion coefficient was with 1.1 x 10^{-8} cm^2/s far under the coefficient for thiamine in the best sustaining matrix on this vitamin which is 2.6 x 10^{-8} cm^2/s in SE S-370. Glycerol dipalmitostearate (Figure 12, C) based delivery systems show the slowest release on all vitamins but incomplete release. After 4 h the release of nicotinamide, pyridoxine and thiamine already reached a plateau but the amount of the released vitamin was only 70 - 90 %. Compared to each other the lipophilic SE S-370 (Figure 12, A) and Glycerol behenate (Figure 12, D) showed similar effects on the vitamins in this multi-particulate system with a particle size of 0.5 - 1.0 mm. The release of all vitamins from all tested matrices is again mainly driven by diffusion.

4.1.5 Influence of sucrose ester concentration

In order to achieve homogenous, sustained release of all vitamins further investigations were made on the effect of the concentration of the lipophilic SE in the matrix. Formulations with either 20 %, 50 % or 80 % SE S-370 were produced by melt granulation and the size fraction 1.0 - 1.6 mm was obtained. A different formation of the matrix structure was assumed by the addition of a higher amount of the hydrophilic compound microcrystalline cellulose expecting that the release behavior of the vitamins changes.

The hardness of the granules changed with altered formulation. The 20 % formulation has much more brittle particles showing high abrasion in this formulation (Figure 13). As it can be seen in Figure 14 (A - C) the release of the vitamins can be controlled depending on the concentration of SE in the matrix. The release rates of the vitamins decrease as expected with an increasing concentration of SE. For riboflavin the diffusion coefficient decreased from D = 1.29 (±0.04) (20 % SE), over 0.22 (±0.01) (50 % SE) to 0.05 (±0.01) 10^{-7} cm²/s (±SD) (80 % SE).

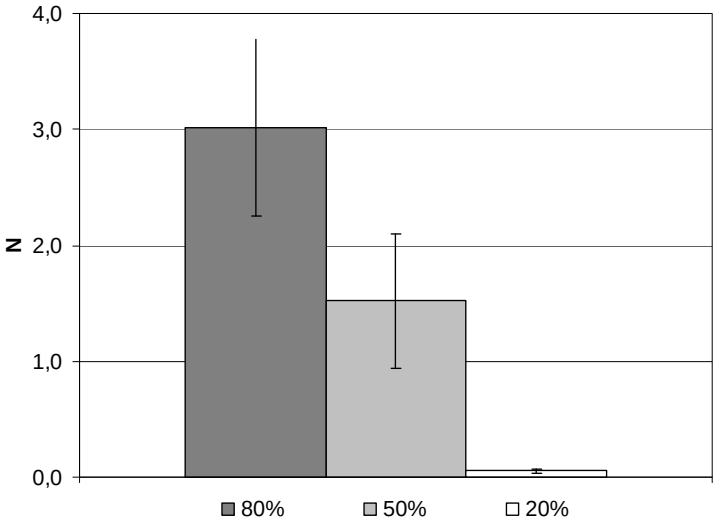


Figure 20. Hardness of granules obtained by melt granulation. Hardness detected by texture analyzer, Granules containing 80 %, 50 % or 20 % SE S-370, 5 % vitamins, filler: MCC. Sieve fraction 0.5 – 1.0 mm.

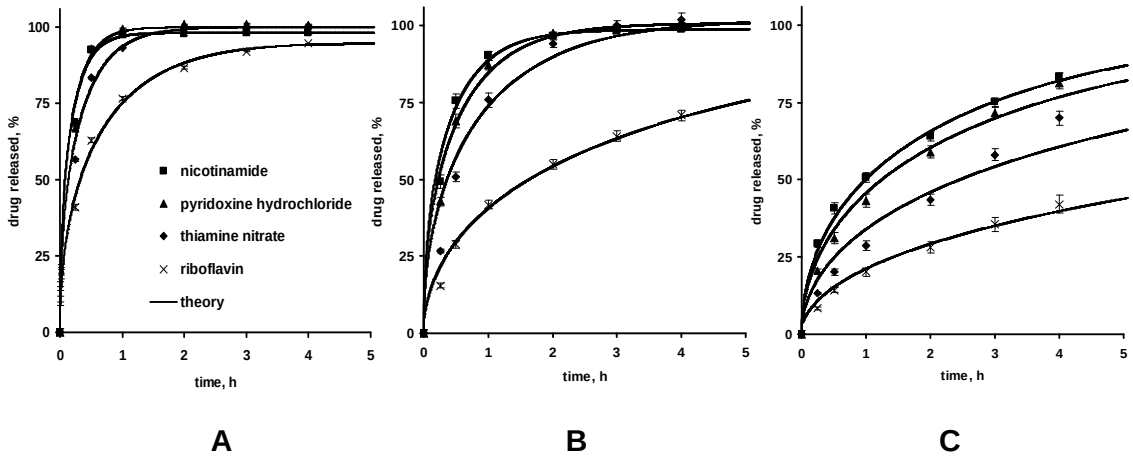


Figure 21. Vitamin release from SE S-370-based granules into phosphate buffer pH 6.8, initially containing: (A) 20 %, (B) 50 %, or (C) 80 % SE (sieve fraction: 1.0 - 1.6 mm, melt granulation) (symbols: experimental results, curves: theory).

Figure 15 shows that the other diffusion coefficients also decrease and approach to a similar level when the content of SE comes up to 80 %. But still the diffusion coefficients keep the same ranking order as seen in the other studies and therefore do not reach homogenous release. However, the variation of the initial SE content allows for an efficient adjustment of desired vitamin release kinetics. Again, good agreement between theory and experiment was obtained, indicating that diffusion seems to be the predominant mass transport mechanism, irrespective of the SE content. But still the molecular weight of the vitamins determines the release from the SE matrix.

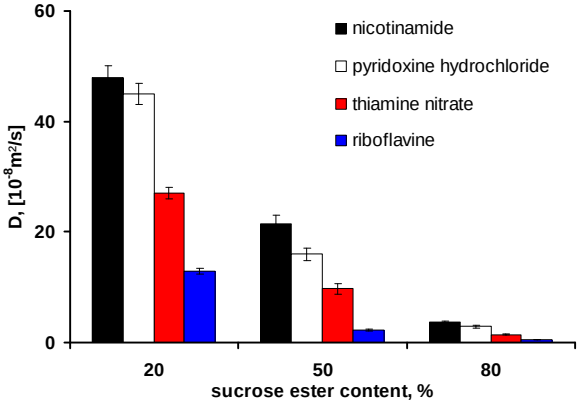


Figure 22. Diffusion coefficients of the different vitamins in phosphate buffer pH 6.8 from granules containing 20 %, 50 %, and 80 % SE S-370 (particle size: 1.0 - 1.6 mm, melt granulation).

4.1.6 Influence of filling agent

The influence of the molecular weight of the vitamins on the release rate can be used as a tracer for the degree of retardation. Ethylcellulose was compared with microcrystalline cellulose to investigate the impact of the filling agent on the release profile. This impact was tested for the SE S-370 in a formulation containing 86 % SE, 9 % filling agent and 5 % vitamins. Microcrystalline cellulose is able to bind high quantities of water between the hydroxyl groups of the amorph parts of the structure [92-94]. In ethylcellulose these hydroxyl groups are partly covered by the ethyl ethers which entail a lower water binding capacity in the structure. In formulations with microcrystalline cellulose a faster dissolution of the vitamins is expected because of the faster water uptake into the matrix. As it can be seen in Figure 16 the release of all vitamins was faster from the formulation containing microcrystalline cellulose compared to ethylcellulose as expected.

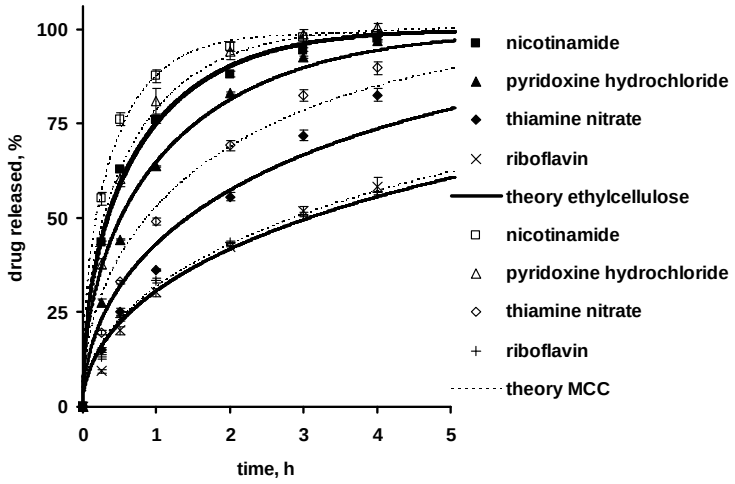


Figure 23. Simultaneous vitamin release from granules prepared by melt granulation into phosphate buffer pH 6.8, containing additionally 9 %: ethylcellulose (closed symbols & solid curves) or microcrystalline cellulose (open symbols and dotted curves) (87 % SE S-370, particle size: 0.5 - 1.0 mm) (symbols: experimental results, curves: theory).

The effect is not very strong due to the low concentration of filling agent in the formulation (9 %). However, it demonstrates that the alteration of filling agents with

different properties is one opportunity to achieve a desired release profile. The effect has not the same extend on all vitamins. Especially for the hydrophilic vitamins the difference between the two filling agents has a much stronger influence on the diffusion coefficient. The difference in MCC and EC decreases from nicotinamide to thiamine with the decreasing solubility of the vitamins. For riboflavin the most hydrophobic vitamin in the study no difference between the diffusion coefficients was determined. Therefore when SE-based formulations are developed the alteration of the filling agent has to be tested for the used API. The release can be accelerated by the incorporation of hydrophilic filling agents when small, hydrophilic substances have to be controlled. For hydrophobic APIs the filling agent has no influence on the release when SE S-370 is used.

4.1.7 Variation of vitamin concentration

In previous studies it has been determined that the release is mainly driven by diffusion. The influence of the total vitamin concentration was investigated in this study by producing samples with 10 %, 12 % and 16 % total vitamin content in the formulation. The results show that no difference on the release profile can be determined for nicotinamide, pyridoxine hydrochloride, thiamine chloride hydrochloride and riboflavin 5'-phosphate (Figure 17). All diffusion coefficients keep on constant levels (Table 8). The vitamin concentration in the granules seems not to affect the matrix structure to accelerate the release in total. The diffusion coefficients still follow the same ranking order as in the other studies before.

Table 8. Diffusion coefficients (in 10^{-8} cm^2/s) (± SD) from granules in phosphate buffer pH 6.8 (80 % SE S-370, melt granulation; sieve fraction: 1.0 - 1.6 mm).

	10 %	**12 %**	**16 %**
Nicotinamide	7.0 (± 2.0)	7.5 (± 0.3)	8.1 (± 1.2)
Pyridoxine hydrochloride	3.8 (± 1.4)	3.8 (± 0.2)	4.9 (± 0.9)
Thiamine nitrate	3.9 (± 1.3)	4.0 (± 0.4)	4.9 (± 1.0)
Riboflavin	1.3 (± 0.2)	1.1 (± 0.4)	1.7 (± 0.4)

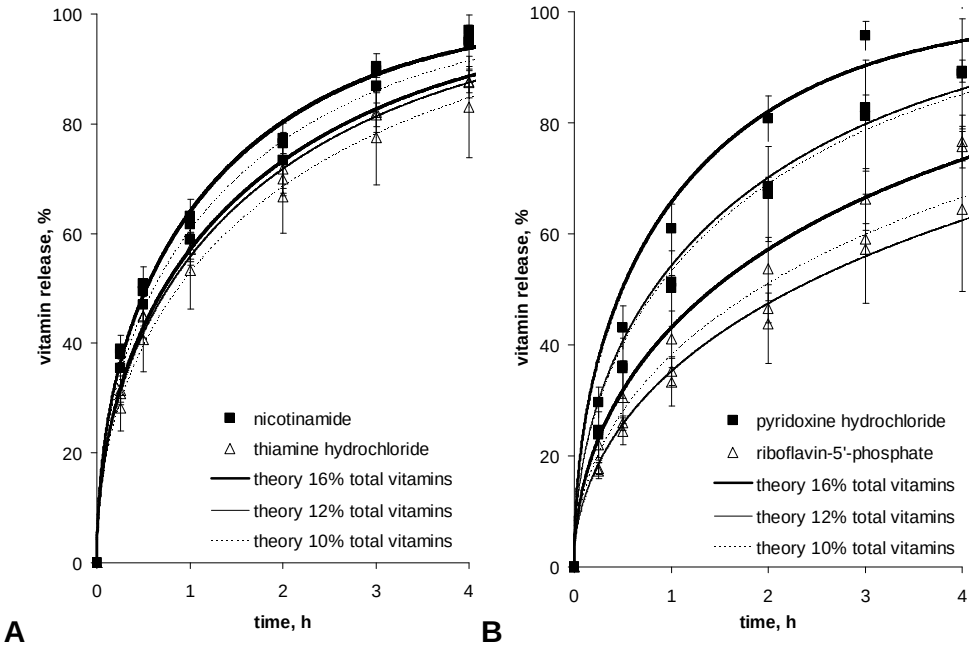


Figure 25. Simultaneous release from granules with different initial total vitamin content (thick curves: 16 %, thin curves: 12 %, dotted curves: 10 % w/w): (A) nicotinamide and thiamine, and (B) pyridoxine and riboflavin release into phosphate buffer pH 6.8 from SE S-370-based granules (melt granulation; SE content: 80 %; sieve fraction: 1.0-1.6 mm) (symbols: experimental results, curves: theory).

4.1.8 Influence of dissolution media on the release profile

Previous release studies have all been carried out in phosphate buffer pH 6.8 as the dissolution medium. In hydrochloric acid or water the release can alter because of the different pH conditions and ionic strengths. The vitamins nicotinamide, thiamine chloride hydrochloride and pyridoxine hydrochloride have no pH dependent solubility. The solubility of riboflavin 5'-phosphate however decreases from 112 g/L in water to 2.5 g/L in hydrochloric acid 0.1 N [31,34].

Previous results showed that the solubility of the substances influences the release but is not the rate-determining step, therefore no differences in the dissolution coefficients of the vitamins in correlation with the pH value of the dissolution medium are expected. The release studies, however, show decreasing diffusion coefficients for riboflavin 5'-phosphate from purified water over phosphate buffer pH 6.8 to

hydrochloric acid 0.1 M. No pH dependency can be discovered comparing the diffusion coefficients of the vitamins (Table 9) (Figure 18).

Table 9. Diffusion coefficients of the vitamins in different release media (in 10^{-8} cm^2/s) (± SD) calculated from the dissolution of granules prepared by melt granulation (80 % SE S-370; sieve fraction: 1.0 - 1.6 mm).

	0.1 N HCl	Phosphate buffer pH 6.8	Purified water
Nicotinamide	7.5 (± 0.4)	8.1 (± 1.2)	9.1 (± 0.6)
Pyridoxine hydrochloride	4.6 (± 0.3)	4.9 (± 0.9)	4.8 (± 0.2)
Thiamine nitrate	4.9 (± 0.4)	4.9 (± 1.0)	3.7 (± 0.3)
Riboflavin	0.5 (± 0.1)	1.7 (± 0.4)	2.5 (± 0.4)

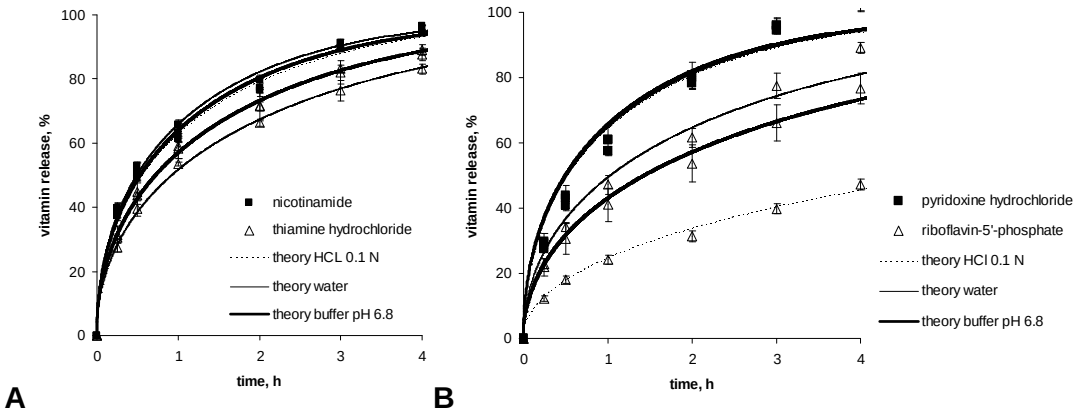


Figure 27. Simultaneous release of vitamins during exposure to different release media (thick curves: 0.1 N HCl, thin curves: phosphate buffer pH 6.8, dotted curves: water): A) nicotinamide and thiamine chloride, and B) pyridoxine hydrochloride and riboflavin 5--phosphate release from SE S-370 based granules (melt granulation, SE content: 80 %; sieve fraction: 1.0 - 1.6 mm) (symbols: experimental results, curves: theory).

The effect of the dissolution medium on riboflavin 5'-phosphate was reported before and interpreted as an effect of pore size, shape and connectivity in the investigated matrix. Addition of surfactant did not improve the drug release rate in these studies [39]. Therefore the solubility of the ingredients did not mainly determine the release rate which agrees with the results of the modeling studies. But the organization of the SE may change in different dissolution media and influence the diffusion coefficient of bigger molecules. When the diffusion coefficients are plotted against the ionic strength of the solutions a dependency for riboflavin 5'-phosphate can be seen whereas the diffusion coefficients of the other vitamins keep constant. Ntawukulilyayo et al. reported an influence of dissolution medium on the release behavior of SE-based controlled release tablets. With higher ionic strength the sucrose stearate S-370 seem to change its self organization after contact with the dissolution medium. The affinity of the polar sucrose head of the molecule to polar liquid is higher in solutions with higher ionic strength and therefore faster orientation in the matrix may occur. Other published studies show that SEs form lamellar and micellar phases in contact with water [7,28]. Especially lamellar phases are exhibited when high concentrations of SE are present. The lyotropic behavior of SEs in solid dosage forms is not well understood and further investigations should prove that the formation of the phases can change with changing ionic strength of the solvent [81].

4.1.9 Storage stability of sucrose ester granule formulations

For the development of pharmaceutical or nutritional preparations it is important that the desired release profile remains stable during the shelf life of the product. Therefore the stability of the matrix is very important. In lipid matrices it is known that aging processes can occur during storage of the product which leads to altering release patterns. To avoid unexpected changes in the release profile the stability of SE-based matrices was investigated. A formulation containing 80 % SE S-370, 15 % MCC and 5 % total vitamins (nicotinamide, pyridoxine, riboflavin and thiamine nitrate) was chosen for this study. Granules obtained by different manufacturing methods and two different SE types were stored at defined climatic conditions for 6 month and analysed for their release patterns (Figure 19). Vitamins are very sensitive to humidity and temperature, therefore the stability of the vitamins during storage was

investigated as well. The influence of the manufacturing method on the release patterns and vitamin stability was found to be very different.

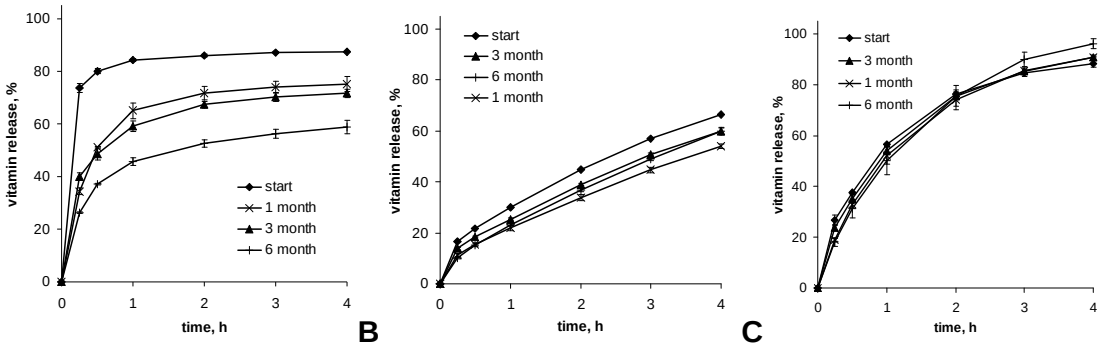


Figure 28. Release of thiamine from wet granulated (A), melt granulated (B) and compressed (C) granules after storage for 6 month at 25 °C/60 % r.h. in PP containers (50 % SE S-370). (Release of all other vitamins, see Annex Figure 9A – 11A).

Wet granulation is unsuitable for vitamins because at the start a vitamin loss of approximately 15 % and during storage further decay of active vitamin can be determined. In the dissolution studies the release seems to slow down. But this effect is caused by lower active vitamin content in the formulation due to degradation. Melt granules show fluctuation of the release rates during storage but the determined 100 % assays keep constant. The matrix formation of molten SE matrices may change during storage time and cause fluctuation in release of the vitamins. Compression is the best method to produce SE vitamin granules. The matrix shows less variability and vitamins show no degradation during storage time. It seems not to influence storage stability of the vitamins and a constant release profile over the tested period of time can be assured. The impact of heat and humidity in the other two manufacturing methods may damage the structures or alter release patterns.

During the first 4 weeks the melt granulated SE S-370 matrix showed a slight ageing process which led to slower vitamin release compared to the day of manufacturing. Afterwards the release rates increased again. For a robust product alteration in release rates is not acceptable. It should be investigated if this fluctuation in release rates can be eliminated through special treatment immediately after manufacturing.

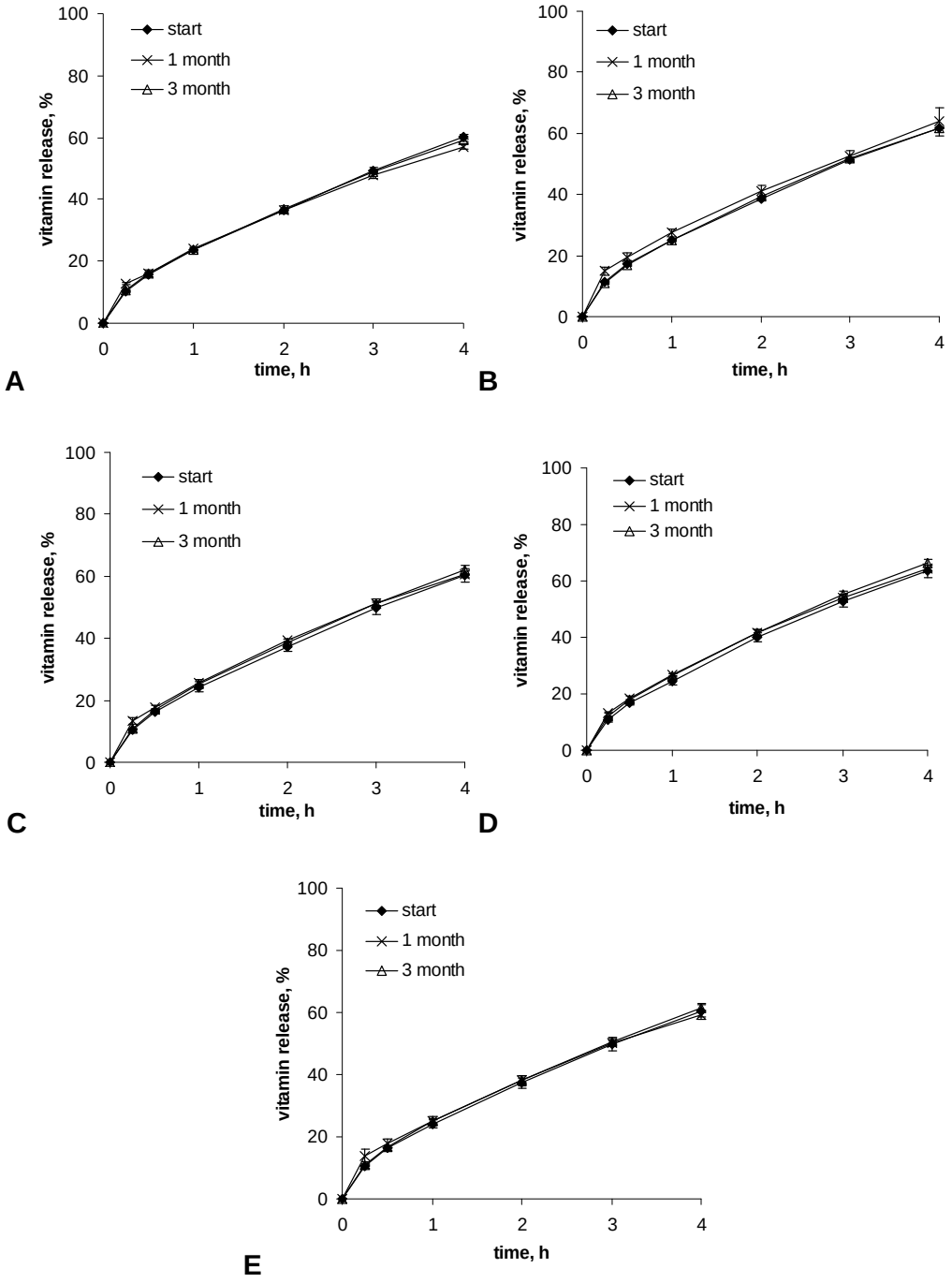


Figure 29. Release of thiamine from granules into phosphate buffer pH 6.8 after tempering at 40 ℃ for 24 h (A), at 30 ℃ for 24 h (B), cooling at 8 ℃ for 24 h (C), freezing at -18 ℃ for 24 h (D) and storage for 3 month at 25 ℃/60 % r.h. or storage at 8 ℃ in the fridge over the whole time (E). (melt granulated, 50 % SE S-370).(For other vitamins see Annex Figure 12 - 14A).

The previous used formulation obtained by melt granulation (80 % SE S-370, 15 % MCC, 5 % vitamins) was produced again. The granules were treated as follows:

- tempering at 40 ℃ for 24 h (A)
- tempering at 30 ℃ for 24 h (B)
- cooling at 8 ℃ for 24 h (C)
- freezing at -18 ℃ for 24 h (D)

All samples were packed in PP containers and transferred to the 25 ℃/ 60 % r.h. climatic chamber after the indicated 24 h.

- One sample was stored at 8 ℃ in the fridge over the whole storage time (E).

All treated samples resulted in constant release rates over three month (Figure 20). It would be expected that the matrix formation changes at different temperatures. Higher temperatures would abet the transformation into the most stable polymorph. Lower temperatures are expected to delay this process. As shown in the DSC studies, SE S-370 does recrystallize very fast when only heated to the liquid crystalline state. This effect seems not to be influenced by treatment subsequent to manufacturing in the tested temperature range. The fluctuation in the previous study may be caused by different particle size distributions in the tested samples.

In the previous study, it was also observed that the incorporated vitamins show rapid decomposition in granules obtained by wet granulation. It should be determined if additional treatment or special packaging can prevent this rapid degradation. The same composition containing 80 % SE S-370, 15 % MCC and 5 % total vitamins was used. Water is known to play an important role in vitamin stability. High water content abets the degradation of vitamins in nutritional supplements. During storage time the packing material is the dominating factor which regulates the water content of the product. Water migration into the container is very different depending on material or packaging form. Today often screw top containers are used for the packing of nutritional supplements. PP tubes are, compared to plastic blister foils, tight to water migration but still not waterproof. Water can migrate into the container during storage

of the product. The containers used have molecular sieve on top of the inner container wall which can absorb the migrated water or dry tablets or granules having high water content. The used CSP tubes can take up water into the molecular sieve. The produced granules (LOD 2.8 %) were packed into CSP tubes. The leftover part of the granules was dried at 40 °C in an air circulating oven until the LOD of 1.2 % was reached. The dried granules were packed into PP and CSP tubes. Therefore the following samples could be compared:

- Granulate dried to LOD 1.2 %, stored in CSP
- Granulate dried to LOD 1.2 %, stored in PP
- Granulate without drying to LOD 2.8 %, stored in CSP
- Granulate without drying to LOD 1.9 %, stored in PP (previous study)

After 1 month storage time big difference between the packing material and the LOD can be observed (Figure 21). LOD of the granules stored in CSP tubes decreased after 1 month to 0.7 % in both samples. This decrease in loss of drying was visible in the stability of the vitamins during storage. Less water in the granules lead to an increased stability of the vitamins in the formulation. This effect can also be observed when the granules were dried to a lower LOD and packed in PP cans. The stability is increased as well in comparison to undried granules in PP from the study mentioned above (D) but still degradation occurs. Drying and storage in containers with desiccant improved storage stability of the vitamins in wet granulated granules. But considering the total amount of vitamin in the formulation, degradation during manufacturing process occurs. The release of the initial content of vitamin is not reached in any of the samples. The same effect can be observed for all vitamins except for nicotinamide which is not sensitive to humidity (see Annex Figure 15A – 17A).

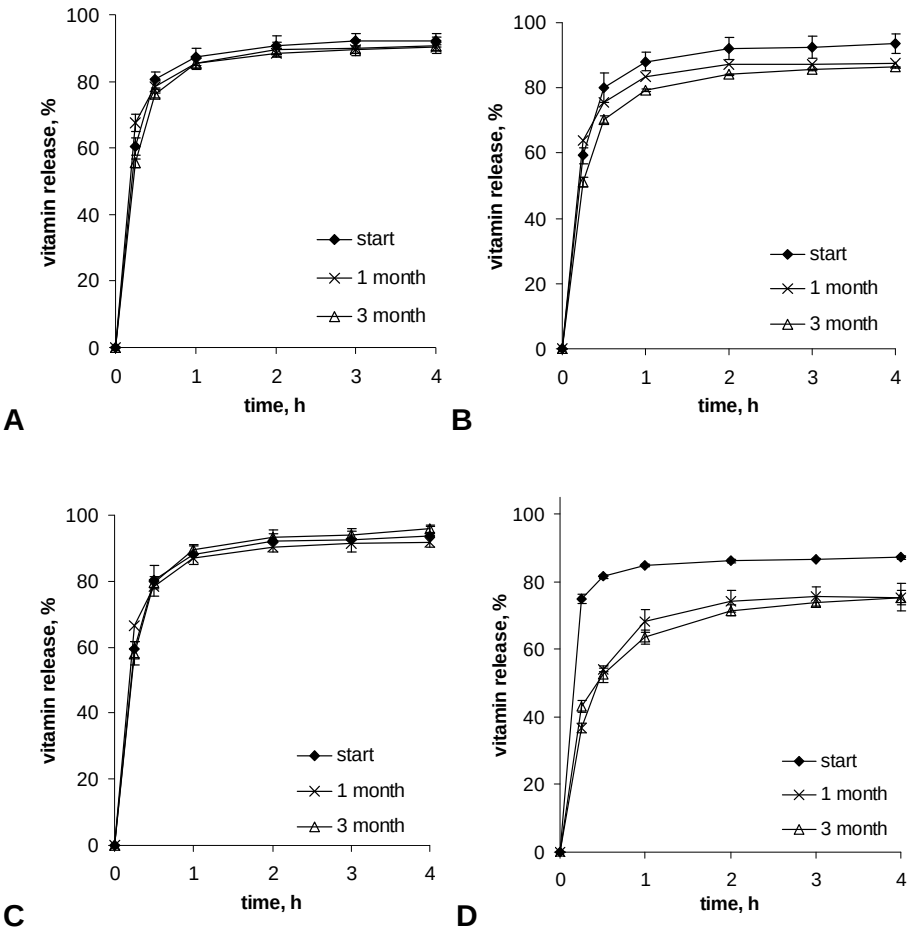


Figure 30. Release of pyridoxine from wet granulated granules initial LOD 1.2 % in CSP (A), LOD 1.2 % in PP (B) LOD 2.8 % in CSP (C) and LOD 1.9 % (D) in PP after storage for 3 month at 25 ℃/ 60 % r.h. (50 % SE S- 370, 45 % MCC, 5 % vitamins).

SE S-370 showed fluctuation in the release rates in untreated samples obtained by melt granulation. It should be determined if the amphiphilic SE S-1170 shows similar behavior over storage time. During storage time both SEs show fluctuation of the release rates (Figure 22). This effect can be caused by particle size distribution of the tested samples or through inhomogeneous distribution of the vitamins in the matrix. The second example is the most probable case because sometimes 100 % is not reached even for the start value.

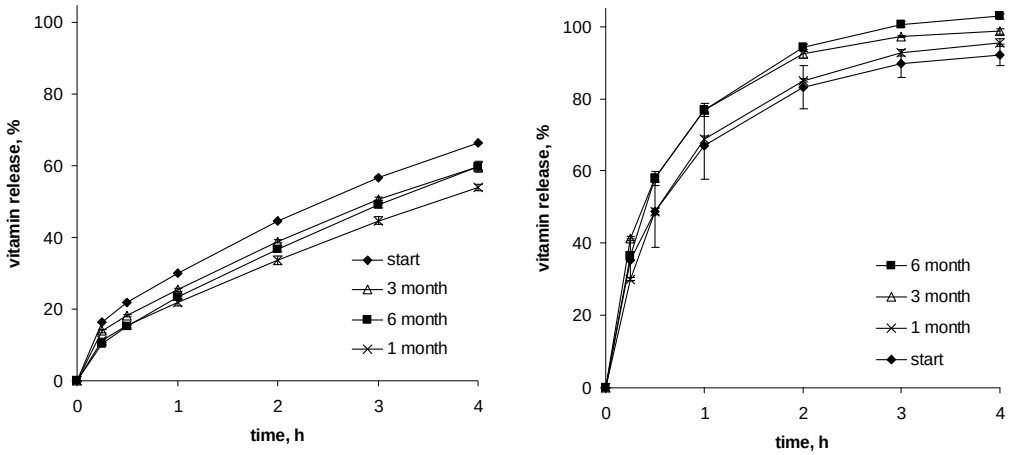


Figure 31. Release of thiamine from melt granulated granules after storage for 6 month at 25 °C/60 % r.h. in PP cans containing 80 % SE S-370 (A) or S-1170 (B), 15 % MCC, 5 % vitamins (for release of the other vitamins from SE S-1170 see Annex Figure 18A).

4.2 Conclusion of granulation studies

Only few publications were dedicated to the field of SEs in sustained release formulations. In this study it could be shown that SE-based formulations are suitable to form multi-particulate system with controlled release patterns. Depending on different parameters a sustained release profile can be achieved. SE concentration and type, sieve fraction of the granules, molecular weight and water solubility of the API, type of the filling agent and the manufacturing method show an influence on the release profile. The aim of simultaneous release profiles of the vitamins nicotinamide, pyridoxine, riboflavin and thiamine could not be achieved. The molecular weight has been discovered to be a dominant value on the release patterns from the SE-based granules. The water solubility influences the release as well but mainly in the beginning of the dissolution time. Therefore a formulation with a simultaneous, sustained release profile containing more than one API would be very challenging. The most probable solution would be to combine actives with similar molecular weight and water solubility. Formulation with erosion control can also be used to achieve this effect. In the case of SEs the diffusion coefficient can describe the different properties of the vitamins because it was shown that diffusion is the predominant mass transport mechanism from SE-based matrices. The type of SE

can adjust the release profile to the desired level. Hydrophilic SEs can be the choice for substances with a high molecular weight instead of lipophilic SEs. As it has been shown for riboflavin the lipophilic SE S-370 only reached a released amount of 50 % after 4 h whereas the more hydrophilic SE S-1170 showed a sustained release profile reaching 80 % after 4 h.

The manufacturing method was found to have a big influence on the release profile and influences the stability of vitamins to a large extent. The use of wet granulation technology should be avoided because vitamins are sensitive to humidity and the residual solvent lead to decomposition and a short stability time. Melt granulation is the most effective method to produce sustained release SE-based granules but can also affect the stability of the vitamins due to the temperatures during manufacturing. In the short term stability studies no sign for damage was determined. Compaction is the gentlest manufacturing method for vitamins. No humidity or high temperatures are needed in the manufacturing process or influence the SE matrix formation which leads to high vitamin stability and constant release patterns over storage time. In an upscaling process reproducibility of the release profile and influence of process parameters should be determined. In the mentioned studies reproducible curves for the laboratory scaled batches were achieved. A variation of process parameters was not possible due to the small scale batches. Product specific variations like the particle size, choice of the excipients and concentration of the matrix forming agent can form a desired release profile using the advantages of a multi-particulate system.

5 Sucrose ester-based mini tablets

Mini tablets can also be a field of application for the obtained granules investigated in Chapter 4. It should be determined if compression into tablets can further extend the release time of the vitamins from the SE matrix. Mini tablets can be filled into capsules or compressed into bigger tablets. They were also selected, because this medication can be swallowed more easily. Mini tablets lower the risk of dose dumping as well as granules or pellets. When one mini tablet fails in functionality not the whole dose of API is available for the body which is extremely important for the safety of a drug product. Usually mini tablets have a diameter of 2 - 3 mm. In this study a tablet diameter of 5 mm was used to investigate the impact of compression on the release patterns. The bigger size was chosen for the reason of further investigation of the matrix forming. The increased size has advantages in the applied methods of analysis. The release mechanism of the API from a known granule matrix can alter during compression. The compression forces can work on the matrix structure and can lead to more dense packing or a new organisation of the SE. The changed shape of the dosage form should also have an impact on the release profile. It was determined in the granulation studies that diffusion is the predominant mass transport mechanism from SE-based granules. The lengthening of the diffusion pathway should slow down the release of the vitamins from mini tablets if diffusion as the predominant mass transport mechanism can be proved again.

The tablet size of 5 mm diameter allows the application of optical methods to characterize the matrix forming behaviour of SE-based formulations. Orange coloured riboflavin 5'-phosphate enables to follow the water penetration into the matrices through optical microscopy because it turns its colour into a bright yellow when it gets in contact with water. Microscopy is a destructive method to follow the water penetration into the tablets and can cause deviations from the true value because of cutting force onto the matrix. Therefore MRI (magnetic resonance imaging) was applied to characterize the water penetration velocity and the interaction of matrix and water during hydration of the tablet.

Matrix formers as sustained release agents are well-known in pharmaceutical applications and are very well characterized considering their erosion and water uptake ability. Especially the hydrogel matrices are well described in the literature.

Matrix forming, erosion and gel layer formation is known for many hydrogel matrix forming substances. These parameters should be known as well for SEs to classify them into the group of hydrogel or lipid matrices. Therefore SE were compared to well-known matrix formers to characterize their matrix forming and release behavior. Big differences in matrix forming could be observed and a new group of matrix formers could be discovered.

5.1 Experimental results and discussion

5.1.1 Influence of sucrose ester concentration

The molecular mass determines the release rate of every single vitamin. Small molecules show higher mobility in the matrix than big molecules. Therefore nicotinamide, pyridoxine, riboflavin and thiamine are released in order of their increasing molecular mass. In previous studies it was determined that the release of nicotinamide, pyridoxine hydrochloride, thiamine nitrate and riboflavin from SE-based granules is driven by diffusion. The release rates decrease by increasing particle size. To determine if the release of vitamins from mini tablets is still driven by diffusion tablets containing either 20 %, 50 % or 80 % SE S-370 were analysed for their release patterns. SE are not free flowing powders and therefore granulation is needed to produce free flowing, compressible tableting mixtures. Melt granulation was chosen for this study because of the good sustained release pattern seen from the granules. Tablets containing 20 % SE show capping or disintegrate within 15 min and therefore cannot control the release over several hours (Release curves see Annex Figure 19A). The tablets containing 50 % and 80 % SE S-370 keep their shape and show sustained release patterns over more than 4 hours. The analytical solution of Fick's second law of diffusion (Equation 2) considering the given initial and boundary conditions could successfully be used to quantitatively describe the simultaneous, controlled release of all vitamins from tablets consisting of 50 % SE S-370, 45 % MCC, and 5 % (total) vitamins (Figure 23, A). Thus, diffusion is the predominant mass transport mechanism in this case. Based on these calculations the following apparent diffusivities could be determined: D = 4.7 (±0.8), 4.4 (±1.1), 3.6 (±1.4), and 0.6 (±0.2) x 10^{-7} cm²/s for pyridoxine H^+, nicotinamide, thiamine cation and riboflavin, respectively. In this case, as it has been shown in previous studies, a correlation between the molecular weight and the release pattern of the vitamins can

be seen. The release rate decreases with an increasing molecular weight in the ranking order nicotinamide > pyridoxine H^+ > thiamine cation > riboflavin. The molecular weight of the active ingredient has a very strong influence on the release pattern from the tested matrices. Importantly, when increasing the SE S-370 content to 80 %, systematic deviations between the analytical solution of Fick's law and the experimental results were observed, indicating that the underlying vitamin release mechanism changed (Figure 23, B). With increasing SE content the release profiles became more and more zero order like. That indicates that no longer only diffusion is the predominant release mechanism when the content of SE has been risen to 80 %.

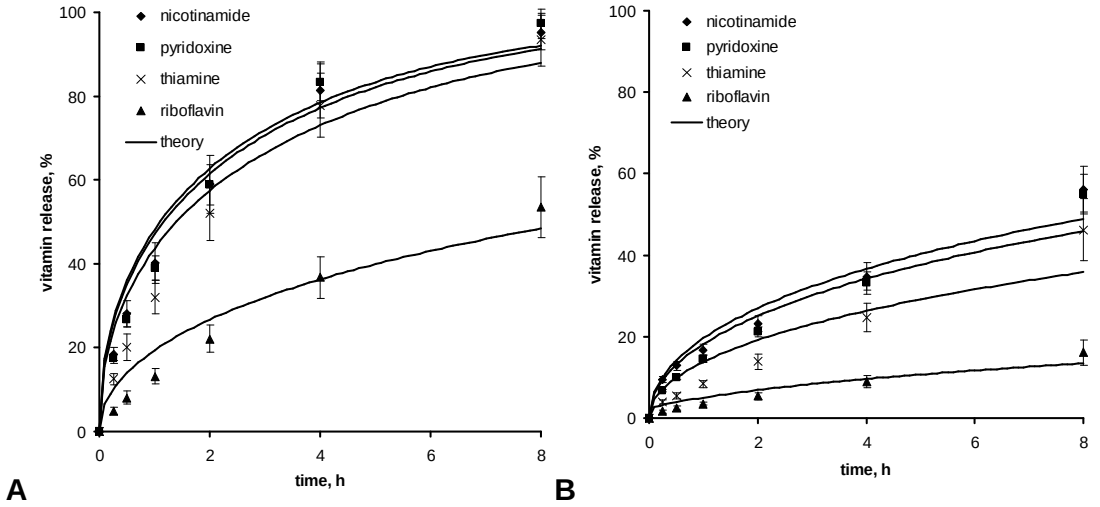


Figure 32. Simultaneous vitamin release from mini tablets into phosphate buffer pH 6.8: (A) 50 % and (B) 80 % (SE S-370; melt granulation) (symbols: experimental results, curves: theory).

5.1.2 Comparison of different manufacturing methods

In granules a big difference in the release patterns between the manufacturing methods was observed. The most retarding effect was seen in the granules obtained by melt granulation. Compression & grinding showed also good retardation but granules obtained by wet granulation showed no effect on the release at all. In this study it should be determined if the same influence of the manufacturing methods after compression into tablets still occurs. To determine the release mechanism of vitamins from mini tablets SE-based granules containing 80 % of SE S-370 were produced again by melt granulation, wet granulation and compression & grinding and

subsequently compressed into tablets. The formulation also contained 15 % MCC and 5 % vitamins. In Figure 24 the release of the vitamins from the melt granulated and compressed granules samples is shown.

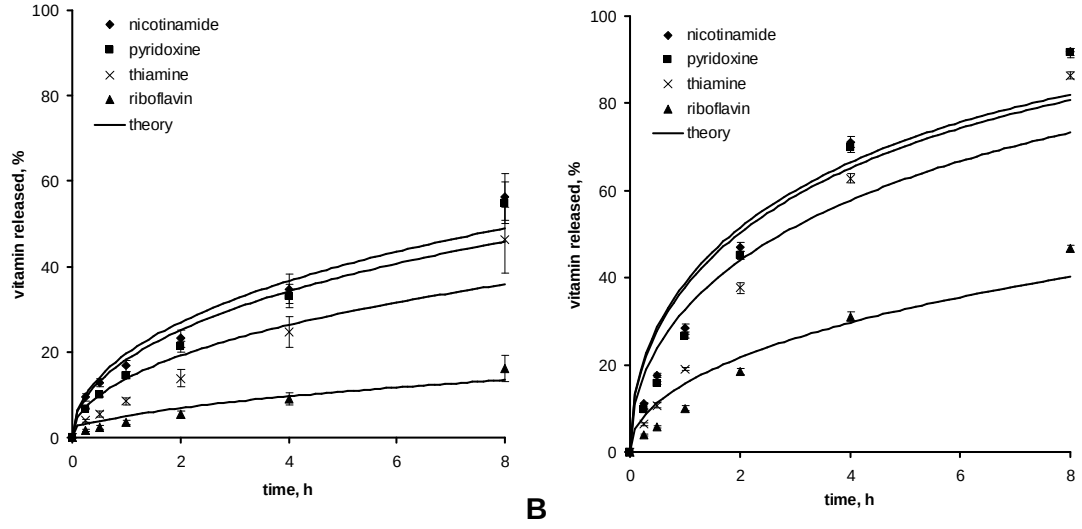


Figure 33. Simultaneous vitamin release from mini tablets based on SE S-370 into phosphate buffer ph 6.8. Type of granule preparation: (A) melt granulation, (B) compression & grinding (SE content: 80 %) (symbols: experimental results, curves: theory).

The release rates from the tablets containing the compressed granules are higher than from the tablets with the melt granulated granules. Again a change in the release mechanism is visible. When granules compressed into mini tablets were obtained by melt granulation it has been shown that the release is nearly zero order like. When the granules are obtained by compression & grinding the mechanism changes and the mini tablets show a release driven by diffusion. Compression & grinding should be preferred to wet or melt granulation for the manufacturing of free flowing powders for stability reasons of the vitamins. Mini tablets obtained from wet granulated granules disintegrated during dissolution and were therefore not modelled for their release kinetics (for release curves see Annex Figure 20A) because the conditions given are not suitable for the application of the solution of Fick's second law due to the erosion of the system.

5.1.3 Influence of sucrose ester type

In order to achieve the same release rates for all vitamins, and therefore overcome the influence of the different molecular weights of the vitamins, the SE type was altered. Lipophilic SEs were determined as suitable matrix forming agents for good water soluble substance in small particles. In granules amphiphilic SEs were not able to sustain the release of the good soluble vitamins. Only riboflavin, the vitamin with the lowest water solubility and highest molecular weight of all used vitamins, showed a sustained release even from amphiphilic SE S-1170. Due to the high release rates in the small particle size of granules no SE type depending effect could be demonstrated in granules. In the bigger particle size of mini tablets it is more likely to determine a difference. The formulation containing 80 % SE was chosen to compare the release profiles from SE S-370, S-550, S-770, S-1170 and S-1670 because the release pattern will be dominated by the high content of SE. The HLB value and therefore the hydrophilicity increases in this ranking order. The chosen manufacturing technique was melt granulation because the most intensive incorporation of the vitamins in the matrix can be achieved with this method. The total vitamin concentration was increased from 5 % to 10 % (nicotinamide, pyridoxine hydrochloride, riboflavin and thiamine nitrate).

The type of SE affects the release mechanism of the vitamins but, astonishingly, it does not correlate with HLB value and hydrophilicity. The release rates for thiamine increase in the following ranking order S-370 < S-1170 < S-570 < S-770 < S-1670 (Figure 25). Nearly the same ranking order can be seen for all other vitamins (Release of all other vitamins see Annex Figure 21A). SE S-570 and S-770 are very close to each other and in some cases change places for the small vitamins nicotinamide and pyridoxine. Comparing the tablet height accession with the release rates the same ranking order can be found. During 8 h of dissolution the height increases by 3 %, 23 %, 29 %, 30 % and 35 %, respective S-370, S-1170, S-570, S-770 and S-1670. The swelling properties of SE seem to have an influence on the matrix forming properties and therefore on the release patterns. Further studies should be carried out to characterize the swelling properties of the different SE types. To get more detailed information about the gel forming mechanism and swelling properties texture analyser studies were carried out.

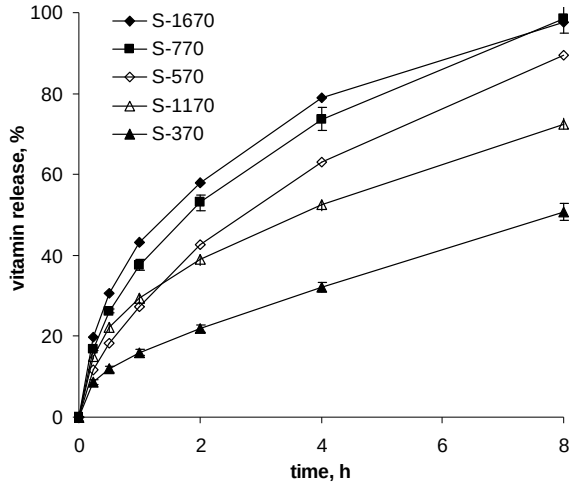


Figure 34. Simultaneous release of thiamine from mini tablets containing different types of SEs into phosphate buffer pH 6.8 (SE content 80 %, total vitamin content 10 %, melt granulation).

It was observed visually that the matrix strength of the SEs is very different. The texture analyser is a good tool to describe this phenomenon [57]. A cylindrical probe was used to determine the strength of the matrices. Table 10 shows the forces needed to compress the matrix structures during hydration. The compression forces on both amphiphilic SE matrices S-770 and S-1170, rise at the beginning and afterwards fall to a constant level whereas the force on the lipophilic SE matrix keeps nearly constant over the dissolution time of 480 min. The initial hardness of the tablets containing SE S-1170 is slightly higher than the other tablets but taking this into account it still shows the highest rising in the compressing force at the beginning.

Table 10. Maximum force on flat-tipped cylindrical probe resulted by compression of mini tablets containing SE S-370, S-770 and S-1170 (SE content: 80 %).

Force [N]	**0 min**	**15 min**	**30 min**	**60 min**	**120 min**	**240 min**	**480 min**
SE S-370	15	13	13	12	12	12	8
SE S-770	13	18	15	9	4	3	2
SE S-1170	20	32	26	23	15	1	1

With the cylindrical probe the different matrix stiffness can be described but the true hydrated layer thickness of the tablets cannot be displayed because there remains compressed tablet compound between the probe and the dry tablet core. With increasing dissolution time the tablet softens that also the lower hydrated layer of the tablet is compressed during the measurement. For the determination of the layer thickness the probe was changed to a needle. SEs form a stiff matrix compared to HPMC or HPC which is why the needle probe can recognize the contact with the hydrated tablet surface. The tablets containing SE S-370 and S-550 could not be analysed with the needle probe because the difference in the hardness of the hydrated layer compared to the dry tablet core is very small therefore the point of contact to the dry tablet core could not be determined. For tablets containing SE S-770, S-1170 and S-1670 analysis was possible. The force which indicates the contact of the dry tablet core was determined to be 0.5 N. At this point the sudden increase of the time-force-curve starts when the needle hits the dry tablets core. This force was determined by the comparison of texture analyzer data and digital picture analysis (See chapter 5.1.4). Figure 26 shows the layer thickness in the amphiphilic SE matrices at different points in hydration time. Comparing the three SE matrices, a difference in the velocity of water penetration can be detected.

SE S-770 and S-1670 perform very similar. Water penetration in S-1670 is faster because of the higher hydrophilicity of the matrix structure. The case of SE S-1170 is different. In the beginning water penetrates very fast into the S-1170 matrix even faster than into S-1670. But then it seems to form a stiff narrow matrix which slows down water penetration into the inner regions of the tablet for the first 30 - 60 min which can be the cause of the slower release from these matrices. Subsequently penetration accelerates again after 1 h of hydration. This phenomenon indicates once more a difference in matrix forming mechanism between the different SE types.

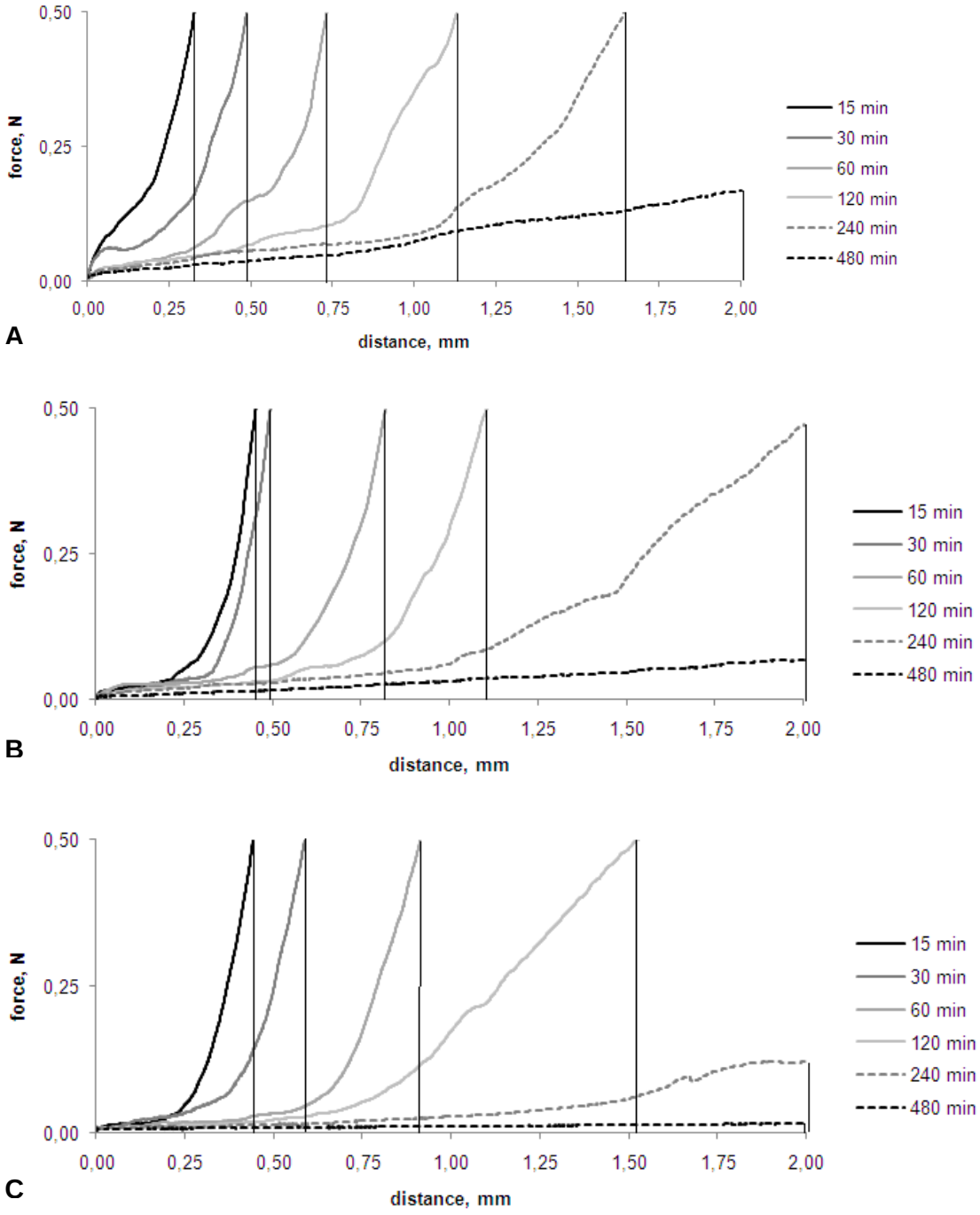


Figure 36. Results from texture analysis showing the force/distance curves of the needle probe after 15, 30, 60, 120, 240 min and 480 min dissolution time for SE S-770 (A), S-1170 (B) and S-1670 (C) based tablets. (50 % SE, 10 % vitamins, 40 % MCC)

5.1.4 Characterization of matrix forming in sucrose ester-based tablets

For the characterization the formulations containing 50 % matrix former, 40 % MCC and 10 % total vitamins were used. Nicotinamide, pyridoxine hydrochloride, riboflavin 5'-phosphate and thiamine chloride hydrochloride were chosen as the active ingredients. Granules were obtained by compression & grinding and compressed into mini tablets with a diameter of 5 mm. The hydration of these formulations should be faster and higher amounts of water are expected to penetrate into the systems. To compare SE-based tablet matrices with well-known matrix systems also mini tablets containing hydrogel or lipid matrix formers were obtained (Table 11). The comparison of identic compositions can help to learn more about the matrix system of SEs and perhaps can be characterized to be a part in the group of hydrogel or lipid matrix forming systems. The following matrix formers were used in this study:

Table 11. Matrix formers used in the study for characterization of the matrix forming process. Applied formulations: 50 % matrix former, 40 % MCC and 10 % vitamins.

Lipid matrix former	SE	Hydrogel matrix former
Glyceryl behenate	S-370	HPC
	S-770	HPMC
	S-1170	Polyacrylic acid

With the chosen formulations diffusion controlled release was achieved. Astonishingly, the release from these different formulations is nearly identical for all vitamins (Figure 27) (Release of pyridoxine and riboflavin 5'-phosphate see Annex Figure 22A). Thiamine, the only vitamin with permanent, positive charge is the exception. Its release is much slower from the negative charged polyacrylic acid because of ionic bondages between the molecules. With different methods it should be determined if the matrix forming behavior is also as similar as the release patterns or if there are big differences between the systems. At least a difference between the lipid matrix former and the hydrogel formers is expected.

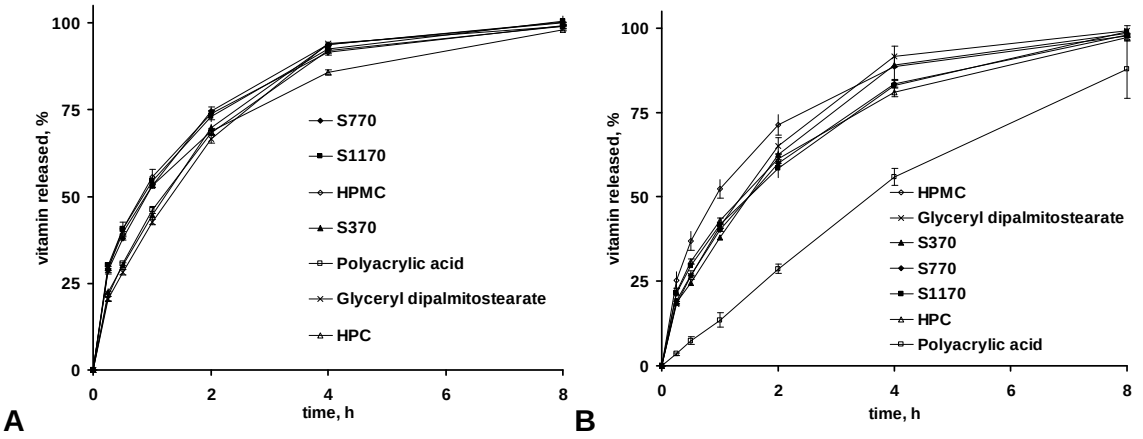


Figure 38. Release of nicotinamide (A) and thiamine (B) from matrix mini tablets containing 50 % matrix former, 10 % total vitamins and 40 % MCC granules obtained through compression & grinding.

In order to describe and compare the different matrix systems digital picture analysis was combined with MRI to better describe the matrix forming mechanism of different SEs. Erosion and water uptake was quantified to analyse the differences in water binding capacity and erosion control. Images of all tablets were taken at predetermined points in time during hydration in phosphate buffer pH 6.8 and measured with digital picture software. NMR imaging provides an opportunity to monitor non-invasively swelling and hydration processes. Additionally, the interaction of water with the matrix forming substances can be visualized with this method.

Hydrogel matrices are described very well in the literature. They show extreme swelling properties up to 200 % of their former size. The formation of an outer swelled layer and an inner rubbery region characterize hydrogel matrix tablets. Due to extreme swelling of the outer regions only little amounts of water can penetrate into the core and form the rubbery region in the centre which leads to very little mobility of the active ingredient in the rubbery region and slow release from the matrix system [48]. In lipid matrices the hydrophilic-lipophilic interaction determines the velocity of water penetration into the matrix and diffusion of active ingredient out of the tablet.

In NMR images regions of high interaction of water and matrix structures are pictured in white and regions of low interaction or dry parts in grey or black. In Figure 28 the hydration processes of different matrix formers are shown. SE S-770 and S-1170

show similar interaction with water as the HPC and HPMC matrices. SE S-370 and glyceryl behenate are an exception due to the low HLB value. Very low interaction of water and SE S-370 can be detected. Only very little amounts of water penetrate into the system which causes a very low signal which cannot be visualized in the image.

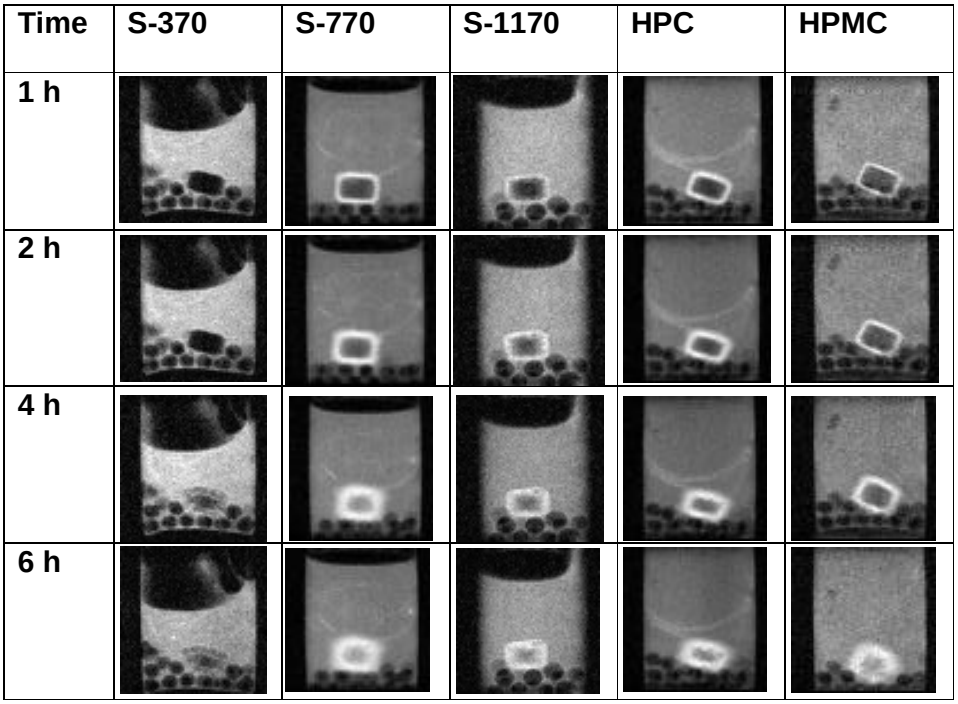


Figure 39. MRI of mini tablets containing 50 % different matrix formers, 40 % MCC and 10 % vitamins.

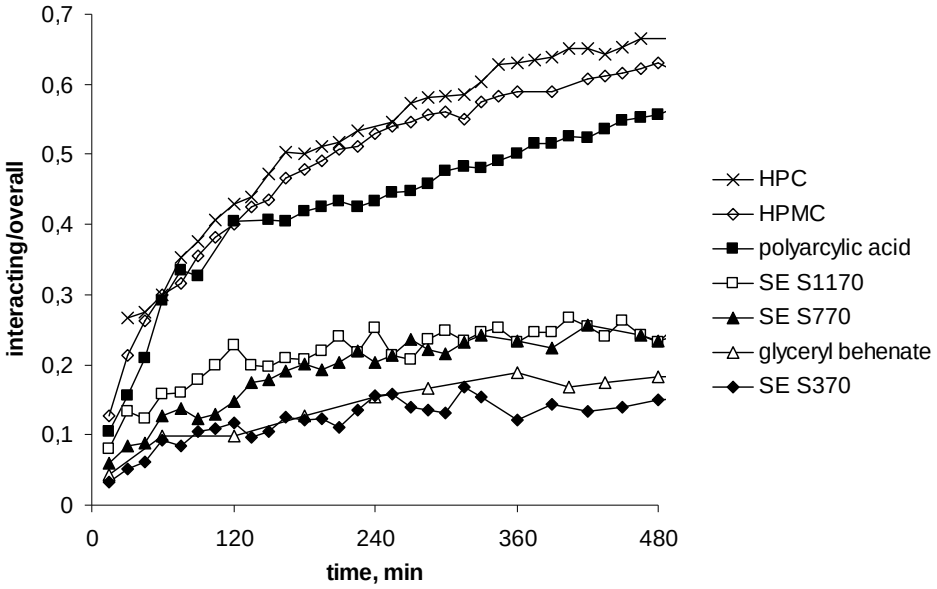


Figure 40. Amount of water, interacting with different matrix systems during hydration over 480 min. Determined by NMR relaxometry analysis.

Analysing the relaxation times of the investigated tablets a differentiation between the hydrogels and the amphiphilic SE can be made (Figure 29). For the detection of the differences in relaxation times, tablets with a diameter of 10 mm were analysed. The signal of the 5 mm tablets was too low to detect differences between the substances. Hydrogel matrices show great interaction with water which increases over hydration time. SEs interact with water on a much lower level. After 4 h the value keeps nearly constant and no further increase can be detected. SE S-770 and S-1170 interact much more with the dissolution medium than SE S-370 and the lipid matrix. In this analysis of the NMR experiments also the interaction between water and the lipophilic matrices could be measured. The interaction was not visible in the image but it can be detected when the samples are analysed for their T_2 distribution over the dissolution period.

When the digital pictures were compared after the same sampling points big differences of water penetration velocity and matrix forming behavior can be observed. The incorporated riboflavin 5'-phosphate is orange coloured in its dry state but when even very small amounts of water get in contact with the substance turns its colour in a bright yellow.

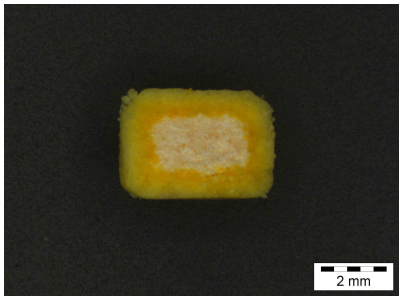


Figure 41. Light microscopic image showing the water penetration front and different concentration zones of riboflavin 5'-phosphate within the tablet.

This fact was used for the determination of water penetration into the matrices. In the image (Figure 30) not only the water penetration front can be followed but also different zones of riboflavin concentration can be observed very well. SE S-370 and S-1170 showed similar behavior in the velocity of water penetration even though the HLB values of the material differ that much (3 and 11)(Figure 31). The diameter of the dry tablet core decreased in the same manner. But remembering the results of the previous investigations of these two SE types, again a differentiation in the matrix

forming mechanism can be made. SE S-370 shows only slight swelling (11 % of its initial height), whereas SE S-1170 extends its height by 19 % after 240 min. After 120 min in SE S-370 and S-1170 tablets there is an outer layer with low concentration, an inner layer with high concentration both penetrated with water and the dry tablet core in the centre. It was still a dry tablet core remaining, whereas the water penetrated already through whole SE S-770 tablets in the same time (Figure 31).

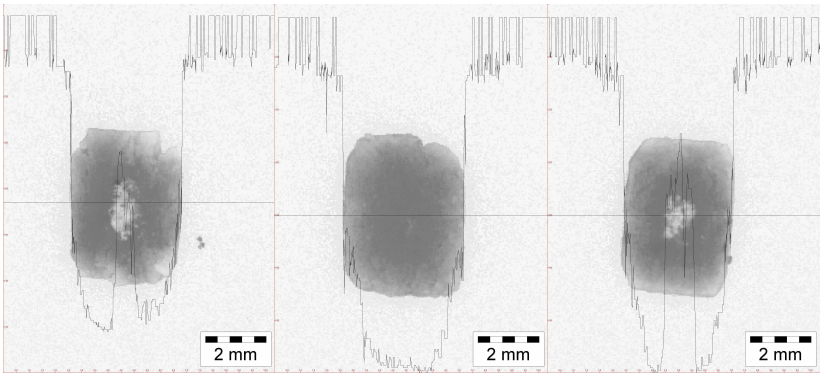


Figure 42. Light microscopic digital images of mini tablets. Tablets containing SE S-370 [a], S-770 [b] and S-1170 [c] after 120 min in phosphate buffer pH 6.8.

Comparing the digital pictures of hydration with the MRIs the interpretation has to be adjusted. Although it was nearly impossible to cut hydrogel matrices in the middle due to their sticky quality when wet and their very soft structure a visual contrast could be observed. The formation of the gel was slightly destroyed during cutting but as described in the literature the gel layer and the rubbery region can be observed. Glyceryl behenate and SE S-370 performed similar during hydration concerning their swelling properties. There is an increase in height about 11 % which is mainly caused by the water penetration into the matrix. Both matrices are very brittle and show fine cracks in the structure. The amphiphilic SEs show both more swelling (20 - 23 %) and form a sponge like matrix which, more or less obstruct the active ingredients on their way out of the tablet similar to hydrogel matrices. But the velocity of water penetration into the device is much more characterized through their hydrophilic-lipophilic interaction with the dissolution medium which also determines the release patterns of the actives. The typical gel layer and the rubbery region in the centre can not be observed in SEs (Figure 32).

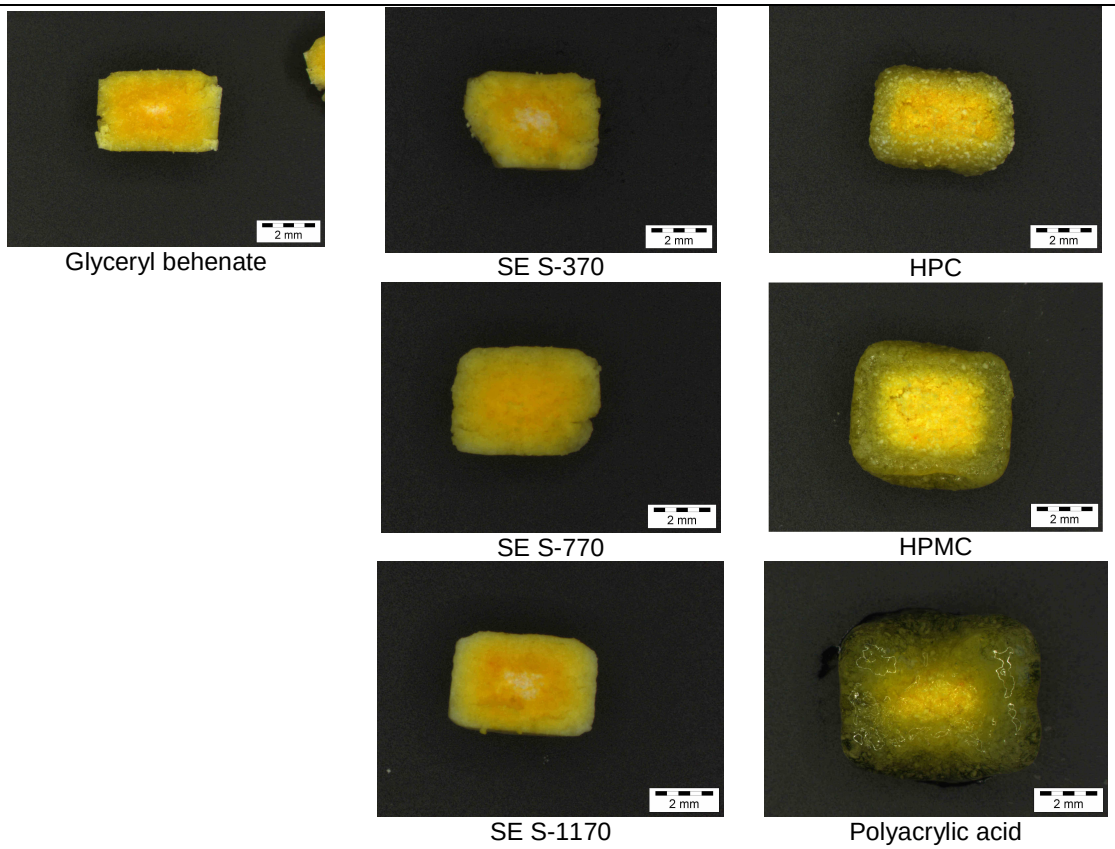


Figure 43. Pictures of mini tablets after 120 min in phosphate buffer pH 6.8 containing 50 % SE, 40 % MCC and 10 % vitamins (granules obtained by compression & grinding)

Quantifying the water uptake into the matrices the reason for this phenomenon can be found. Polyacrylic acid binds high amounts of water into the gel structure, HPMC and HPC also show high water uptake levels but much lower than Polyacrylic acid. SEs do not bind these high amounts of water in their structure. After 60 min in the dissolution medium the hydrogel matrices increased their weight by 460 %, 300 % and 230 % of their initial tablet weight for polyacrylic acid, HPMC and HPC. After 4 h erosion starts which decreases the wet tablet weight again. SEs and the lipid matrix increased their weight only to 120 %, 130 %, 140 % and 150 % for glyceryl behenate, SE S-370, S-770 and S-1170. In Table 12 the water uptake is compared to erosion in percent of the initial tablet weight. From this data it can be verified again that SEs are not like hydrogel matrices but are much more similar to lipid matrices in the matrix forming behavior. Again it can be seen that the amphiphilic SEs S-770 and S-1170 form a group of matrices which show both, higher water uptake with swelling of the

matrix but no formation of gel layers as a release barrier for APIs. All formulations showed only slight erosion. This is mainly caused by the dissolution of the vitamins which account for 10 % of the formulation. All tested mini tablets were obtained from granules produced by compression & grinding. The release from melt granulated granules is expected to be slower as it has been in previous studies. This can be caused by an altered hydration process or hydration velocity. To determine the difference in matrix behavior between mini tablets obtained from melt or compression & grinding granules, the previously investigated SE formulations were obtained again through melt granulation and were subsequently compressed into mini tablets. The release is slower as from the mini tablets obtained from compressed granules, as expected (Figure 33). Hydration was followed again with digital pictures at predetermined time points. In Figure 34 images of the different tablets after 1 h in phosphate buffer pH 6.8 show the reason for the slower release patterns. The velocity of water penetration is much slower compared to the compressed granule mini tablets what lead to a slower dissolution of the vitamins. During melt granulation the SEs pass into the liquid crystalline state. The formation of the molecules changes and prevents the water from hydrating the matrix.

Table 12. Increase of tablet weight through water uptake and decrease of dried weight through erosion of mini tablets containing different matrix forming agents during 480 min in phosphate buffer.

	Increase of weight through water uptake [%]	**Decrease of weight through erosion/dissolution [%]**
Glyceryl behenate	24 %	11 %
SE S-370	34 %	15 %
SE S-770	97 %	12 %
SE S-1170	80 %	20 %
HPC	214 %	20 %
HPMC	345 %	33 %
Polyacrylic acid	733 %	62 %

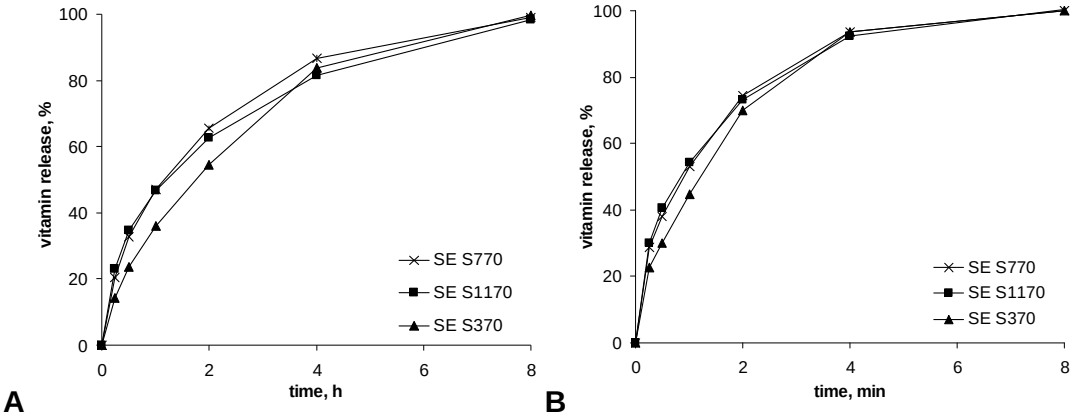


Figure 45. Release of nicotinamide from mini tablets. Granules obtained by melt granulation (A) and compression & grinding (B) containing 50 % SE S-370, 40 % MCC and 10 % vitamins (error bars are within the symbols) (for release of the other vitamins see Annex Figure 23A).

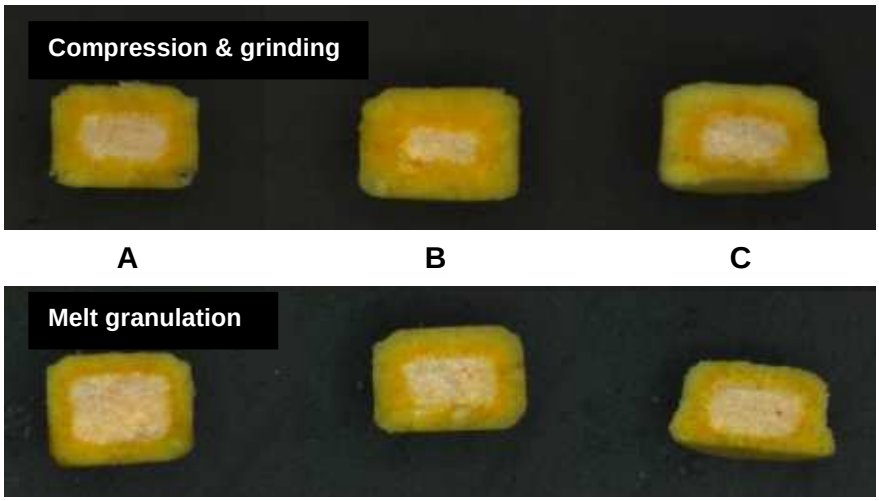


Figure 46. Images of mini tablets (upper row: granules obtained by compression & grinding; lower row: granules obtained by melt granulation) after 60 min in phosphate buffer pH 6.8 containing 50 % SE S-370 (A), S-770 (B) and S-1170 (C), 40 % MCC and 10 % vitamins.

5.1.5 Storage stability of sucrose ester-based mini tablets

In the following study the stability of SE matrices concerning the constant release patterns of the active ingredients from the dosage forms were investigated. Two formulations were tested for their release patterns. The matrix of the formulations contained 80 % SE S-370 and 20 % MCC. To this matrix, vitamins of either 10 % or

20 % of the total matrix weight were additionally added. The vitamins chosen were nicotinamide, pyridoxine hydrochloride, riboflavin 5-phosphate and thiamine chloride hydrochloride. Again the mechanism from a 80 % SE-based mini tablet formulation remained zero order like for all vitamins. The mini tablets were stored in PP screw top containers. After manufacturing and after 3 month storage at 25 ℃/60 r.h. the mini tablets were analysed (Figure 35). The zero order profile still remained after short term storage. No alteration of release patterns were detected with either high or low content of vitamins. Comparing both release curves of nicotinamide it can be considered that a high vitamin content or high content of soluble substances leads to faster release from an identic composed matrix. After 4 hrs either 38 % or 50 % nicotinamide are released from the matrix. All other vitamins showed the same effect. It is very likely that the dissolved substances form pores in the structure of the SE matrix which accelerates the diffusion of the water into the matrix as well as the diffusion of the vitamins out of the matrix. When dissolution of APIs influences the release rate from SE-based systems also the solubility of excipients is expected to have a strong impact on the release profile. This influence is tested in chapter 6.1.3.

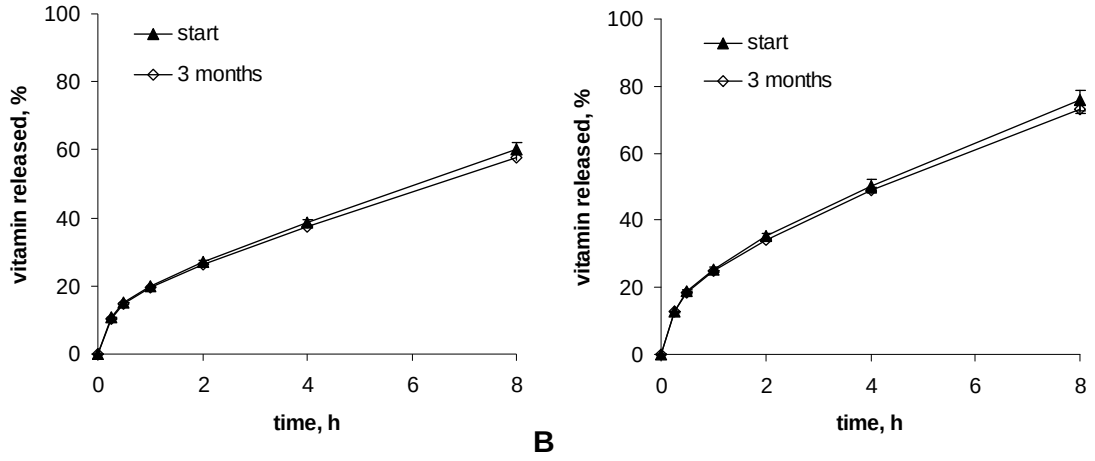


Figure 47. Nicotinamide release from mini tablets into phosphate buffer pH 6.8 after manufacturing and after 3 month at 25 ℃/60 % r.h. Total vitamin content 10 % (A) or 20% (B) of the matrix weight. (Composition of the matrix was kept constant at SE S-370 80 %, 20% MCC) (for release of the other vitamins see Annex Figure 24A).

5.1.6 Discussion of results from mini tablets

The release profiles of multiple vitamins from SE-based mini tablets altered in dependency on the SE concentration as it was shown for SE-based granules. A change in the formulation from 50 % to 80 % SE S-370 did not only change the release rate but also change the release mechanism when melt granules were compressed into mini tablets. In the 50 % SE formulation the release was driven by diffusion but in the 80 % SE formulation a nearly zero order profile could be achieved. The same happens when comparing the manufacturing methods. When the 80 % formulation is melt granulated the release is nearly zero order like as mentioned before. When the granules are obtained by compression & grinding the release mechanism changes again to diffusion controlled release. The applied manufacturing method can be used to adjust the release to the desired profile. The amphiphilic SEs can also sustain the release of good soluble substances from mini tablets. Physico-chemical properties of the API are the critical factors for the choice of the SE type.

In comparison to hydrogel or lipid matrix formers SEs form a separate group of matrix forming systems. The formation of the SE matrix can be described like lipid matrices especially for the lipophilic types but in the amphiphilc types also swelling occurs. The formation of a stiff, spongy matrix can be observed unlike the formation of gel layer in hydrogel matrices or no swelling at all in lipids. The swelling properties, matrix structures and the velocity of hydration of the SE types changed in dependency to their HLB value. SE S-1170 is an exception in this range. This SE type seems to sustain the release in an additional mechanism within the matrix which could not be discovered yet. The interaction with water was lower than in SE S-770 which could be caused by the formation of lyotropic structures within the tablet. The self-orientation of SEs may play an important role in matrix forming in solid dosage forms. When the hydrophilic and lipophilic parts of the SEs are oriented in the matrix structure the formation of lamellar structures could hinder the penetration of water into the dosage form. When the vitamins are embedded within a cubic mesophase the release is expected to be very slow because the very polar vitamins would not penetrate through a hydrophobic barrier to a high extend. Especially thiamine with its permanent positive charge would go through the hydrophobic layer of SEs. The release from the different matrix formers in the tested concentration is very similar, although the matrix formation is very different. Due to Different SEs molecules the

formation of the liquid crystalline mesophases is expected to be different. In the characterisation studies in chapter 3 lamellar and cubic structures were detected in the SEs S-770 and S-1170. In SE S-370 none of these structures were seen. Amphiphilic SEs can be an alternative to other well-known matrix formers due to their application in different granulation methods. The release can be adjusted to the desired profile by varying the SE concentration, type and the manufacturing method.

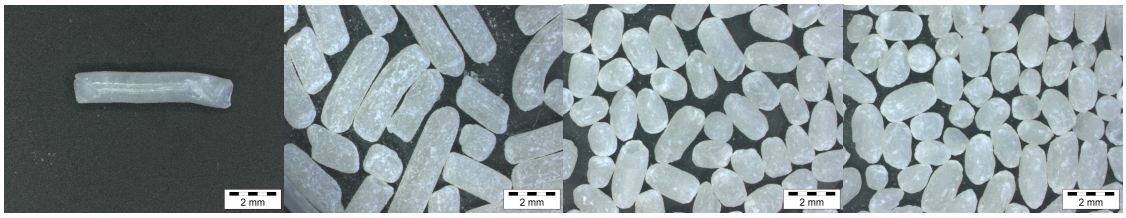
6 Sucrose ester-based pellets

Melt extrusion is a continuous process which enables to reduce costs in manufacturing. The hot melt extrusion process can be used to produce solid dosage forms which can be further processed in different ways [95-97]. Granules can be subsequently compressed into tablets or spheronization can form spherical shaped pellets for capsule filling or other applications. Pellets have the advantage of very good flow ability and narrow particle size distribution. This is very important when diffusion as the predominating mass transport mechanism in melt extruded SE-based particles remains. The diffusion pathways have to be constant to show reproducible release from the pellets. For the extrusion of active ingredients often low melting temperatures are needed to avoid decomposition of the API [98]. SEs enter the liquid crystalline state between 50 - 60 °C which can prevent decomposition of sensitive APIs. Twin screw extrusion processes and suitable screw configurations are described in several publications [99-105]. The viscosity of the SEs in the liquid crystalline states depends on the stability of the mesophase and is likely to alter between the different SEs types. But not only adequate melting temperatures are needed to form round and homogeneous pellets. After cooling, SEs form a glassy state which suggests a glass transition covered under the peaks of changing mesophases [21]. Usually polymers are used to form melt extruded pellets. The polymers have to show glass transition at a specified temperature (T_G). In this state the polymer is flexible and can be formed without loosing its shape after cooling of the extrudate. Over the T_G the polymer is amorph and soft. After cooling the amorph state is kept but the particles stay in the spherical form. Lipids recrystallize after melting but can be formed to pellets in the softened state. Good knowledge of the behavior of used substances is necessary to develop a reproducible, robust process. To determine the release mechanism ideal spheres should be produce to get as close as possible to the estimated conditions. The shape factors of the resulting pellets can be analysed in different ways [104,106-108]. In this study a video camera-based system was used to determine the shape characteristics. The sphericity, diameter-length ratio and the particle size distribution can be used to characterize the quality of the samples. In the following study it was determined if SEs are suitable for the melt extrusion/spheronization process and which parameters should be considered when processing these substances.

6.1 Experimental results and discussion

6.1.1 Finding and optimization of spheronization process parameters

To get knowledge about the behavior of SEs during the extrusion/spheronization process, pure substances were processed at different extrusion and spheronization parameters. The extrusion temperature was set to 55 ℃ for the SEs S-370, S-770 and S-1170. After the feeding zone a zone of transport elements was inbuilt. Two zones of kneading blocks followed, divided by a short transport zone. At the end, a feeding-to-the-die zone finished the screw configuration (die diameter: 1.6 mm). This configuration was kept over all extrusion studies. The resulting strands were manually broken into smaller pieces (Figure 36, A) and afterwards spheronized at different speeds to investigate the impact of speed on the resulting yield and spherical form. The strands were spheronized for 10 min at all tested speeds.



A **B** **C** **D**

Figure 48. Pictures of extruded and spheronized SE S-370 pellets, A = Extrudate, B = spheronized for 10 min at 300 rpm, C = spheronized for 10 min at 600 rpm, D = spheronized for 10 min at 900 rpm.

The spheronization speed of 300 rpm did not lead to spherical shaped particles (Figure 36, B). The strands were broken into smaller pieces during spheronization and the ends were slightly rounded. They lost only 7 % of the initial weight. At a rotation speed of 600 rpm the result was much more satisfying. The length of the particles was shorter and egg-shaped pellets were achieved but the mass loss rose to 54 % in this sample. The rotation speed of 900 rpm brought the best result of the study concerning particle size distribution (Figure 37) and also the sphericity reached 0.925 for SE S-370 (Table 13). But in contrast, the mass loss reached the unacceptable value of 82 %.

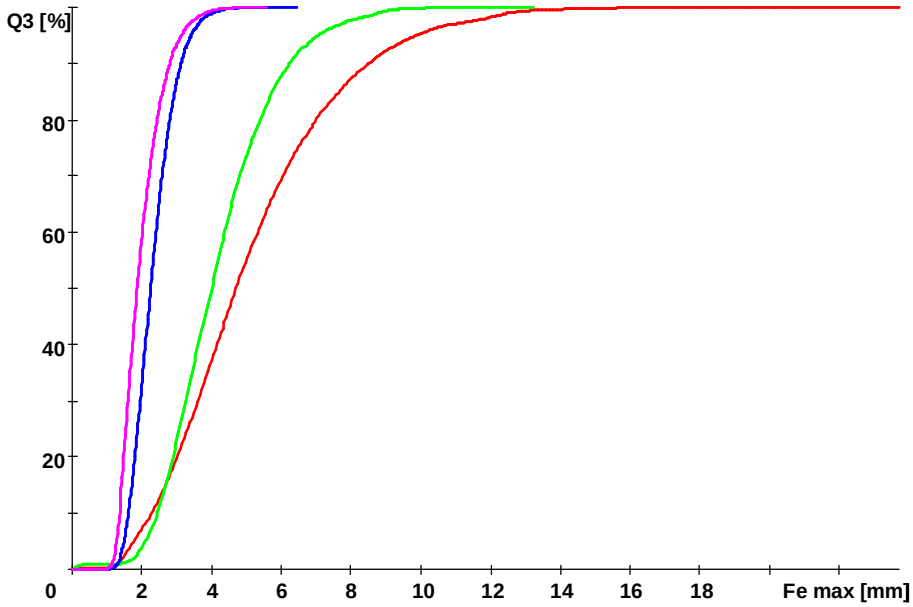


Figure 49. Particle size distribution of SE S-370 pellets spheronized for 10 min at 900 rpm (pink line), 600 rpm (blue line), 300 rpm (green line) and without spheronization (red line) (room temperature).

Table 13. Yield, L/D ratio and sphericity of different SE pellets (100% SE).

	speed, rpm	yield, %	mean L/D ratio	mean SPHT (sphericity)
SE S-370	300	93	2.247	0.741
	600	46	1.517	0.910
	900	18	1.412	0.925
SE S-770	300	95	2.336	0.706
	600	62	1.580	0.896
	900	16	1.379	0.933
SE S-1170	300	96	2.193	0.721
	600	63	1.493	0.906
	900	19	1.511	0.896

The results of the studies on SE S-770 and S-1170 brought similar results (For images, particle size distribution and shape characteristics, see Annex Figures 25 - 28A). With an increasing spheronization speed the shape characteristics of the pellets can be improved. But with increasing speed also the mass loss rises. The rotation speed of 600 rpm was determined as the standard speed for SE pellets. All tested SE types reached a value for sphericity of ~0.9 at this speed which is promising for the spheronization of SE-based formulations (Table 13). The achieved yield of 50 – 60 % has to be improved in further studies. The optimisation of spheronization time was the first option to get more spherical shaped pellets and to reduce mass loss to an acceptable level.

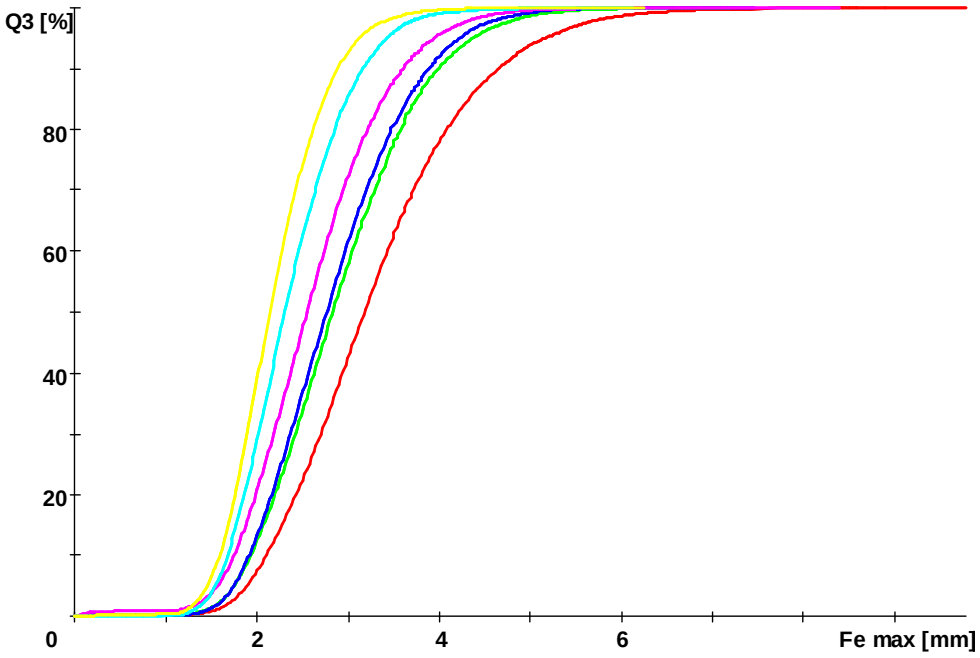


Figure 51. Particle size distribution (A) and sphericity (B) of pellets based on SE S-770 spheronized at 600 rpm for 2 (red), 5 (green), 7 (blue), 10 (pink), 15 (light blue) and 20 (yellow) min, (at room temperature)

Pure SE S-770 extrudates were spheronized at 600 rpm for 2, 5, 7, 10, 15 and 20 min to determine the shape of the resulting pellets as well as the yield (For images of the resulting pellets and shape characteristics see Annex Figure 29 - 31A). Fe_{max} characterizes the maximum length of the pellets. Figure 38, A shows that the

Fe_{max} distribution decreases at increasing spheronization times resulting in steeper distribution curves for longer spheronized pellets. The sphericity of the pellets also increases with longer spheronization time (Figure 38, B) resulting in decreasing Q_3 (SPHT<0.9) of 74 % after 2 min to 21 % after 20 min. As expected, continuous decrease of resulting yield with increasing spheronization time was observed. Further extension of the spheronization time would probably produce even better results concerning sphericity and particle size distribution but after 20 min the yield was only 42 %.

Additionally, it has to be taken into account that 80 % of the resulting pellets had a sphericity over 0.9 which is good for pure SE substance. Further spheronization would increase the mass loss but would also decrease the diameter of the pellets. Decreasing c_{min} (characterizing the pellet diameter) indicates the abrasion of the pellets during spheronization. The breakage of extrusion strands in the spheronizer always leads to spheres because the sphere is the mechanically most stable geometrical form. The average pellet diameter decreases with increasing spheronization time. After 20 min only 93 % of the diameter after 2 min spheronization time remains. It could also be observed that after leaving the extrusion die SE strands increase their diameter while cooling. The used die diameter was 1.6 mm but the pellet diameter after 2 min spheronization is 1.72 mm which is an increase of 7.5 % during cooling. This phenomenon is described in chapter 6.1.6.

The wall of the spheronizer can be heated during the spheronization process. High temperatures can soften the matrix and help to form spherical shaped pellets. To test the influence of spheronization temperature the double jacket of the spheronizer was adjusted to room temperature (~25 °C), 40 °C and 60 °C by the circulation of heated water in the double jacket. The diameter of the pellets stayed constant at 1.7 mm at all temperatures, which indicates that no abrasion occurred during spheronization for the duration of 10 min at 600 rpm. The yield of pellets having a sphericity >0.9 increased from 46 % over 49 % to 62 % from RT over 40 °C to 60 °C. But in contrast the Fe_{max} increased as well. 50 % of the pellets had a length <2.5 mm at RT, <2.6 mm at 40 °C and <2.9 mm at 60 °C. The spherici ty of the pellets can be approved by higher wall temperatures but the breaking of the strands into isometric shaped particles is prevented (For shape characteristics, see Annex Figure 32A). As a result of the pure SE extrusion study, the extrusion temperature of the substances

was set to 50 - 56 °C. This temperature range is likely to rise when non-melting substances are added to the formulation. Standard spheronization parameters were set to 600 rpm and a spheronization time between 7 - 12 min. The sphericity and the particle size distribution can be optimized when increasing the spheronization time but this leads to high mass loss. Further optimization of the pelletizing process is needed which is why different pelletizing methods have to be investigated to optimize isometric breakage of the strands and therefore improve the sphericity of the pellets.

6.1.2 Pelletizing methods

In established manufacturing processes the extruder is often followed by a pelletizer which breaks the extrudates in square pieces. This arrangement eliminates the erratic breakage of the extrudates in the spheronizer. It should be determined, if the mass loss during spheronization can be reduced by using different pelletizing methods. The extrudates were cut manually from the extruder directly after leaving the die using a spattle (Die diameter 1.5 mm). The extrudates were also broken through an oszillating sieve and milled in a ball mill to find out which pelletizing method is the most effective and increases the yield of the spheres. The tested formulation contained 80 % SE S-1170, 15 % tricalcium phosphate and 5 % total vitamins (nicotinamide, pyridoxine hydrochloride, riboflavin and thiamine nitrate).

*Table 14. Yield and size distribution of pellets (*80 % SE S-1170, 15 % tricalcium phosphate and 5 % total vitamins*).*

Pelletizing method	**yield, %**	**δ c_{min} at Q_{30}=90 % - c_{min} at Q_3=10 %, mm**	**δ Fe_{max} at Q_{30}=90 %- Fe_{max} at Q_3=10 %, mm**
oszillating sieve	29	0.47	1.36
ball mill	60	0.24	1.82
simulated pelletizer	65	0.24	0.87

The strands were cut directly from the die when warm or they were cooled down to room temperature before they were transferred to the sieve or mill. In this cooled

state the strands are very brittle and splitter when force is put onto them. The yield of the samples broken by the oszillating sieve was far the lowest in the test. In the sieve erratic breakage occurs. The strands do not only break cross, they also break lengthwise and form needle shaped particles which cannot be parted by a sieve and can not be rounded in the spheronizer. In the ball mill less abrasion on uneven breakage is observed. Therefore the main mass loss occurs in spheronization. The highest yield is determined for the direct pelletizing at the extruder die (Table 14). No mass loss occurs during cutting. The strand is still soft and shows not brittle splittering. It can be cut easily in short pieces. The manual method leads to nearly square pieces and shows that immediate cutting increases the yield of the spheres. Comparing the resulting shape parameters also big differences can be observed (Table 15). Regarding the average L/D ratio of the samples, the oszillating sieve would be the best method but taking into account the high mass loss throughout the process and the highest standard deviation of the factor, it is not the chosen method to improve the spheronization process. The ball mill produces more homogenous pellets but they are very long. During milling they do not break into square pieces. The lowest mass loss during the process and a high L/D ratio with low standard deviation occurs only in the simulated pelletizer sample.

*Table 15. Shape characteristics of pellets (*80 % SE S-1170, 15 % tricalcium phosphate and 5 % total vitamins)*. In brackets the Q_3 (SPHT>0.95) is indicated.*

Pelletizing method	**mean L/D ratio**	**mean SPHT**	**Q_3 (SPHT >0.9), %**
oszillating sieve	1.39	0.93	79 (49)
ball mill	1.64	0.88	45 (20)
simulated pelletizer	1.37	0.95	91 (54)

The differences in the shape parameters can even be detected visually (Figure 39). Pelletizing directly from the die is the best method to achieve round pellets with the lowest mass loss during processing. The L/D ratio could be optimised when higher batch sizes are processed which leads to a continuous, homogenous flow of the extrudate. When a constant flow rate is achieved an automatic pelletizer can be used

to cut the extrudates in square pieces. The size distribution of the pellet length shows the most homogeneous and narrowest distribution for the simulated pelletizer (Figure 40) but the mean length of the pellets is still too high (1.8 mm) due to manual cutting.

Figure 54. Spheres after pelletization and spheronization using the pelletizing methods oszillating sieve (a), ball mill (b) and the simulating pelletizer (c). Containing SE S-1170 80 %, total vitamins 5 % and tricalcium phosphate 15 %.

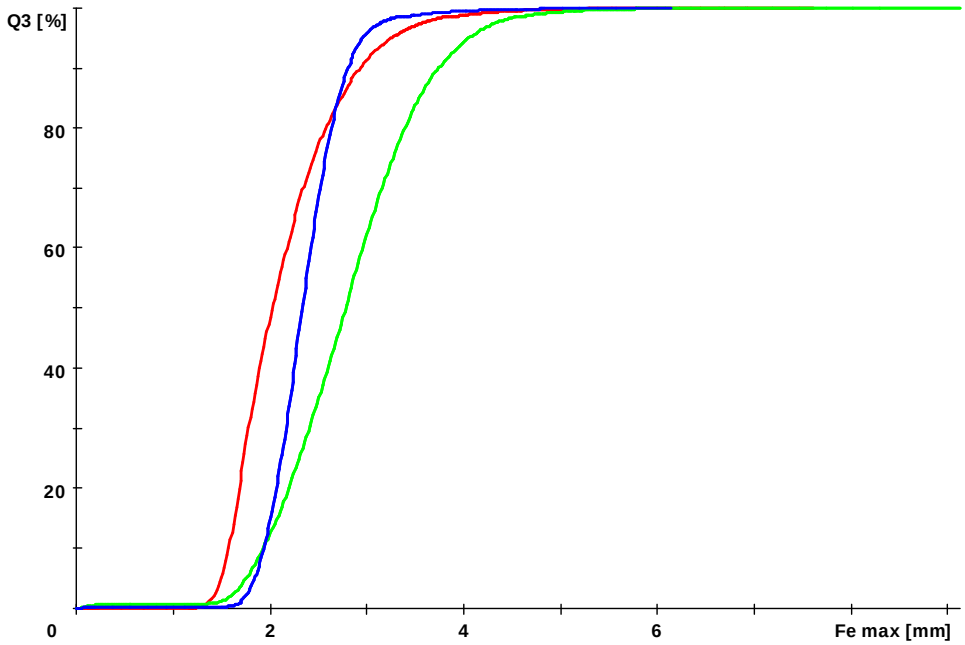


Figure 55. Particle size distribution of spheronized pellets using different pelletizing methods. Oszillating sieve (red line), ball mill (green line) and the simulating pelletizer (blue line) (sphericity see Annex Figure 33A).

6.1.3 Impact of excipient on the spheronization result

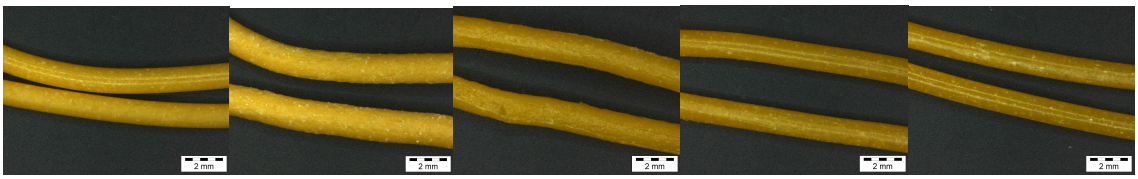
To improve mechanical stability of the pellets during spheronization process spheronization aid was added to a formulation containing 70 - 90 % SE S–770 and 5 % total vitamins. The spheronization aid content was modified between 5 - 25 % PEG 6000. The extruded strands were again manually broken into shorter pieces and subsequently spheronized for 12 min at 600 rpm.

Table 16. Shape characteristics of pellets containing different levels of PEG 6000 as spheronization aid in the formulation.

PEG 6000	yield, %	c_{min} Q_3= 50 %, mm	Fe_{max} Q_3= 50 %, mm	mean SPHT	mean L/D
5 %	65	1.52	2.14	0.91	1.49
15 %	73	1.57	2.32	0.90	1.56
25 %	75	1.58	2.08	0.93	1.41

The yield and c_{min} at Q_3 = 50 % indicate that the mechanical stability of the pellets is improved by the addition of increasing amounts of spheronization aid (Table 16). But looking at the shape characteristics and the length of the pellets no correlation between level of spheronization aid and shape can be made. The difference in yield and c_{min} is very low between 15 % and 25 % spheronization aid content which shows that the increase of spheronization aid from 15 % to 25 % has only a very little effect. The length of the particles is highest in the sample with 15 % and the sphericity and L/D value is worst. These results show that the spheronization aid level of 15 % is the optimum in this formulation. The mechanical stability is increased to the highest level leading to non-abrasive, non-breaking strands (For more results of shape characteristics, see Annex Figure 34 - 35A). When extrudates are pelletized directly behind the die and the breakage is not left to the spheronization process this formulation would build the most stable pellets with low abrasion values.

Different substances were tested to determine the influence of the used fillers on the pellets. Formulations containing 80 % SE S-770 and 5 % total vitamins (nicotinamide, pyridoxine hydrochloride, riboflavin and thiamine nitrate) were tested with 15 % SMCC 50, tricalcium phosphate, PEG 6000, starch or glucose as fillers. As early as in the extruded strands (Die diameter 1.5 mm) differences can be observed (Figure 41). Tricalcium phosphate can be observed as white dots on the extrudate, the surface of these strands is very rough. PEG 6000 is molten and shows the most homogeneous strands. In this sample, defects on the surface can be observed. High extrusion temperature or high extrusion speed can have caused these surface defects. All other extrudates have a smooth surface but the suspended particles can be seen through the opalescent, glassy structure of the SE matrix in all samples.



A **B** **C** **D** **E**

Figure 57. Images of extrudates containing SMCC 50 (A), Tricalcium phosphate (B), PEG 6000 (C), starch (D) or glucose (E) as filler (15 %). SE content 80 %, total vitamins 5 %. Die diameter 1.5 mm.

Mass loss after spheronization for 7 min at 600 rpm was only 30 - 35 % for all formulations. The analysis of the diameter c_{min} of the pellets showed that tricalcium phosphate forms the most stable extrudates. All other formulations show decrease of pellet diameter during spheronization. The resulting spheres were very similar. The manual cutting method allowed no differentiation between the particle distributions. Therefore the length of the particles was not analysed. All pellets had a mean sphericity of 0.88 to 0.93 which is very close to the aspired 0.95. All pellets were tested for dissolution patterns to investigate the influence of the excipient on the release profile of the vitamins from melt extruded pellets.

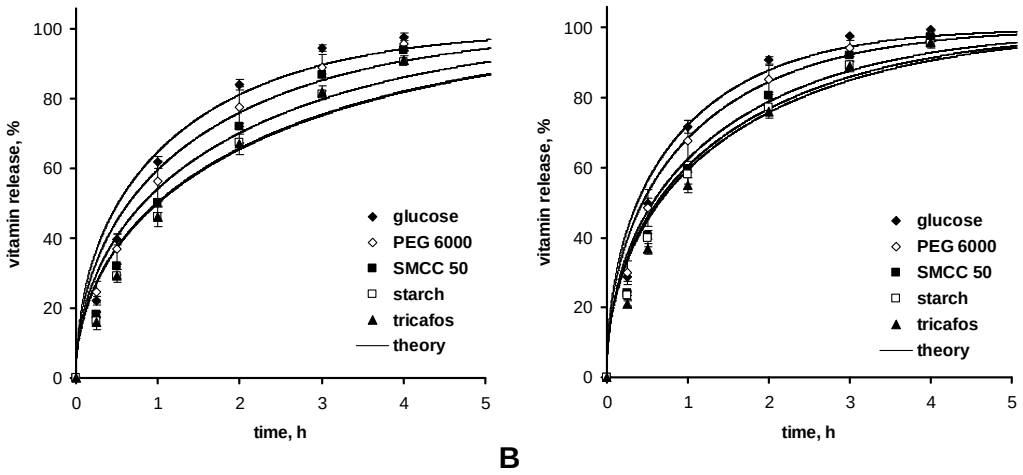


Figure 58. Release of thiamine (A) and pyridoxine (B) from pellets containing different fillers (initial die diameter 1.5 mm, total vitamin content 5 %, SE S-770 80 %; filler 15 %: SMCC 50, tricalcium phosphate, PEG 6000, starch and glucose. (symbols: experimental results, curves: theory) (Release of all other vitamins see Annex Figure 36A)

The release rate decreases from glucose over PEG 6000, SMCC 50 and starch to tricalcium phosphate (Figure 42). Glucose and PEG 6000 are soluble substances which explain the highest release rates from these matrices. The substances dissolve and form pores which lead to accelerated vitamin diffusion out of the matrix. PEG 6000 showed high standard deviation for all vitamins which could not be correlated with a wider particle size distribution (For particle size distribution and shape characteristics of the resulting pellets, see Annex Figure 37 - 38A). All other substances are insoluble and therefore longer release times can be achieved. The release mechanism of the vitamins is mainly dominated by diffusion as it has been seen before in the granulation studies. Again good agreement between the fitting curves and the experiments occurred. The sphere was assumed to be the geometrical form of the pellets (Equation 1). The solubility of the filler had no influence on the release mechanism in SE S-770 based pellets.

6.1.4 Influence of sucrose ester concentration and pellet size

The same formulations known from granulation studies were tested for their application in the extrusion/spheronization process. SE S-370 formulations on the

levels 20 %, 50 % and 80 % SE, MCC as filler and 5 % vitamins (nicotinamide, pyridoxine hydrochloride, riboflavin and thiamine nitrate) were extruded at 58 °C, screw speed: 20 rpm, feeding rate: ~40 g/min, die diameter: 1.6 mm. Extrudates, containing 20 % SE where very fragile and were spheronized at 200 rpm for 5 min (For images of resulting pellets, see Annex Figure 39A). No pellets could be formed from this formulation. Fine powder with a few bigger agglomerates was the result of this test. Both formulations containing higher levels of SE were spheronized at 500 rpm for 10 min. The spheronization resulted in pellets with a mean sphericity of 0.86 and 0.89 and a mean particle length of 2.46 mm and 2.28 mm (Fe_{max} at Q3 = 50 %) for the 50 % and the 80 % formulation, respectively. Q_3 (SPHT<0.9) sank from the 50 % formulation to 80 % formulation from 54 % to 42 %. This means that, in the formulation containing 80 % SE 58 % of the pellets had a sphericity of over 0.90 and still 31 % over 0.95. The particle size distribution was very similar between the 50 % and 80 % formulation (for particle size distribution see Annex Figures 40 - 41A).

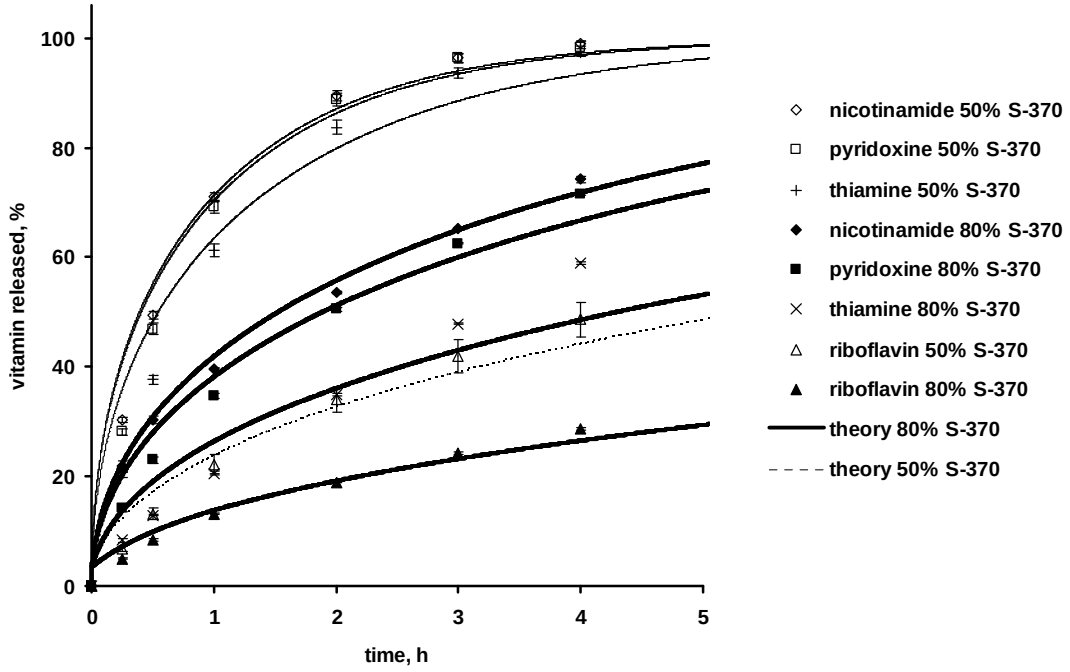


Figure 59. Release of vitamins from formulations containing 50% or 80 % SE S-370 obtained by extrusion/spheronization process (5% vitamins, filler: MCC). (symbols: experimental results; curves: theory)

Again, rising SE levels lead to an increased sustaining effect, as expected, which lead to similar dissolution profiles as obtained by melt granulation (Figure 43). The sustaining effect could even been risen by the addition of other fillers. Riboflavin again was the vitamin on which release the sustaining effect of the matrix was the strongest. The release of the vitamins from both formulations was controlled by diffusion. The 80 % formulation showed the strongest sustaining effect on the vitamins in this small particle size during the studies. The particle size distribution of the pellets is still very wide, which can affect the release patterns of the vitamins. Therefore the formulation containing 80 % SE S-370 was divided in 3 size fractions where the mean pellet length at Q_3 50% was determined to be 1.2 mm, 1.7 mm and 4.4 mm for the 3 size fractions. The sample with the mean pellet length of 1.7 mm showed the best sphericity value. All size fractions, as well as the mixture, were analysed for their release patterns. In Figure 44 the release of nicotinamide and thiamine from the different size fractions and their fitted curves are shown.

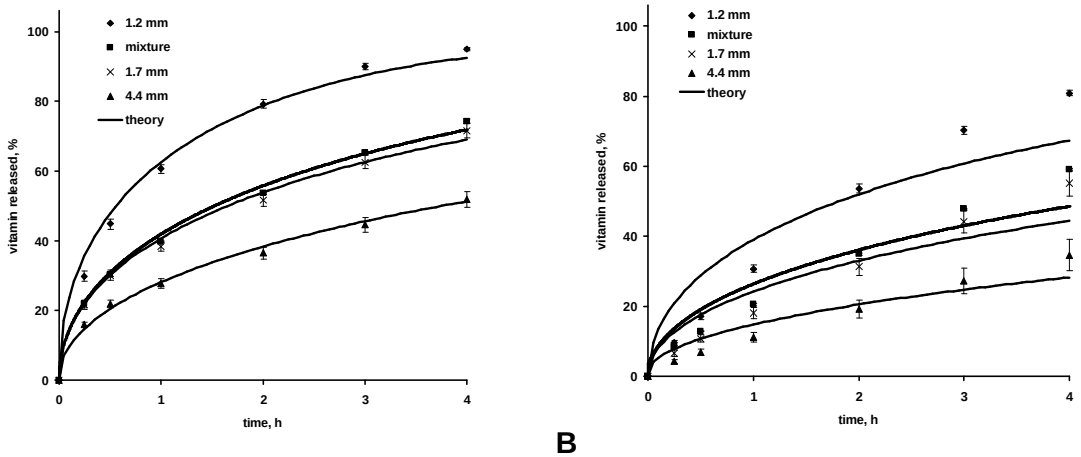


Figure 60. Dissolution profiles of nicotinamide (A) and thiamine (B) from melt extruded pellets divided in different size fractions (containing 80 % SE S-370, 15 % MCC and 5 % vitamins). (Symbols: experiment; curves: theory).

The other vitamins show the same ranking order in release curves (See Annex Figure 42A). As expected the release rates decrease by increasing particle size. Equation 2 for cylindrical shaped particles was chosen to fit the curves to the experiments because of the length of the pellets. The release of nicotinamide, pyridoxine and riboflavin from all particles was controlled by diffusion. The release of thiamine showed deviation from the fitted curves. In this case the release is also

influenced by another phenomenon leading to zero order-like profiles. The mixture of all particle sizes follows very close the release patterns of the size fraction with the ideal diameter fraction of 1.7 mm in all cases. In this sample the wider particle size distribution has no influence on the release behavior of the pellets. The mixture of big and small particles evens out the difference in release patterns. Concerning the influence of spheronization on the size fractions astonishing observations could be made in this study. Figure 45 shows the impact of spheronization on the pellet length and diameter in the size fractions. All pellets were spheronized at the same time and afterwards divided into the size fractions, therefore similar abrasion effects were expected on all pellets. Narrow distribution for the small particles and wider distribution for the bigger particles was found, as expected. When analysing the diameter the results were vice versa indicating that abrasion during spheronization happens mainly on the small particles.

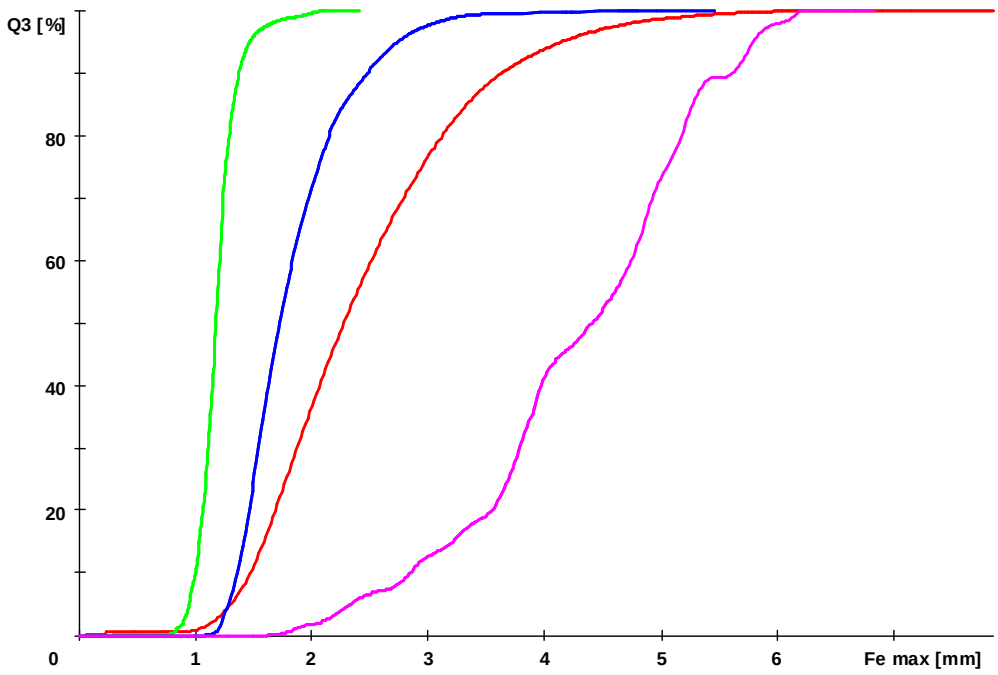


Figure 61. Particle size distribution of pellets divided in different size fractions (containing 80 % SE S-370, 15 % MCC and 5 % vitamins). Red line: mixture of all fractions, green line: 1.2 mm, blue line: of 1.7 mm, pink line of 4.4 mm mean pellet length.

The mean diameter of the size fractions rises from 0.9 mm over 1.5 mm to 1.6 mm in size fraction 1.2 mm, 1.7 mm and 4.4 mm. The distribution of the diameter sinks in the same order as the mean diameter rises. This leads to a decreasing diameter compared to the initial die diameter and leads to a wider particle size distribution because longer pellets show nearly no abrasion at all (mean diameter 1.5 – 1.6 mm, used die: 1.6 mm). Pellets in the size fraction <1.0 mm are therefore mainly crushed parts of breaking strands and should be eliminated from other pellets by sieving. Again, it was shown that in the spheronization of SE-based pellets it is necessary to cut the strands directly after leaving of the die because erratic breaking of the strands lead to a wide particle size distribution and low yield of optimal pellets.

6.1.5 Influence of sucrose ester type

The variation of the SE type is expected to change the release patterns from the pellets as seen for the concentration of the SE. It was shown in granules that the amphiphilic SE S-1170 was not able to sustain the release of nicotinamide, pyridoxine or thiamine from melt granulated granules. For this study S-370, S-770 and S-1170 were the chosen SE types. Again a formulation containing 80 % SE, 15 % MCC and 5 % total vitamins was investigated. Extrusion/spheronization parameters were set to 58 °C extrusion temperature, die diameter: 1.6 mm, spheronization for 10 min at 500 rpm. Spheronization lead to similar shaped particles for all SEs. The mean pellet length was 2.3 mm, 2.4 mm and 2.4 mm, sphericity was 0.89, 0.88 and 0.9 for SE S-370, S-770 and S-1170. In extrusion/spheronization process sustained release over 3 - 4 h was achieved for SE S-770 and S-1170 (Figure 46). The choice of more hydrophobic and insoluble fillers can sustain the release even further as shown for the granules and the pellet studies (See chapter 4.1.6 and 6.1.3). The release from SE S-370 based pellets resulted in the slowest release, as expected. The release of thiamine from SE S-370 was again nearly zero order like as it has been seen in the studies above. The transport of this most polar molecule in the most lipophilic SE is again influenced by other effects and shows deviation from the fitted diffusion curve. From the spherical shape of the dosage forms similar release kinetics as from the granules were expected. During melt extrusion the SEs are brought into the liquid crystalline state and a homogeneous strand results. In melt granulation parts of crystalline powder are incorporated in the

granules. These parts can lead to an accelerated release compared to melt extruded pellets. (For images of the resulting pellets, see Annex Figure 43A).

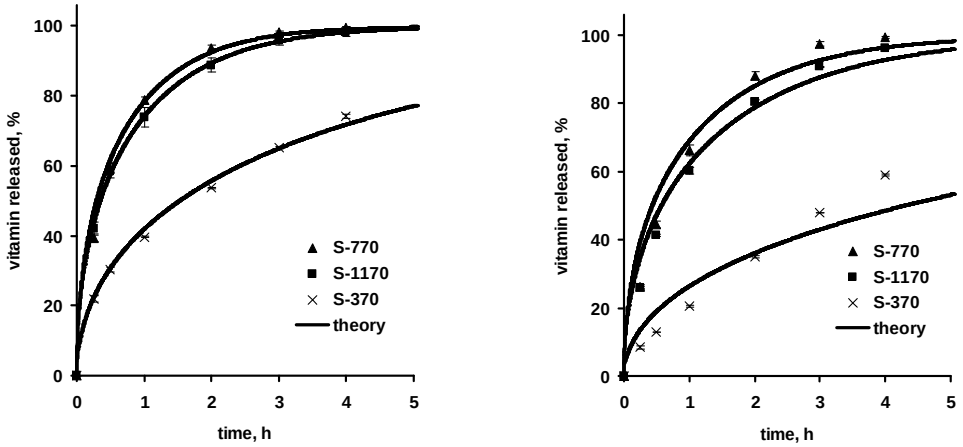


Figure 62. Release of nicotinamide (A) and thiamine (B) from SE-based pellets obtained by extrusion/spheronization (SE content 80 %). (Symbols: experimental results; curves: theory). Release of all other vitamins, see Annex Figure 44A)

6.1.6 Impact of manufacturing parameters on the release profile

Extrusion temperature or speed can influence the liquid crystalline mesophase during processing of the SEs and lead to different matrix structures. The influence of extrusion temperature was tested using a formulation containing 70 % SE S-370, 10 % PEG 4000, 15 % starch and 5 % total vitamins. The mixture was extruded at 50 ℃, 55 ℃ and 60 ℃. All extrusion temperatures lead to homogeneous soft strands but the optimum for this mixture would be 55 ℃. At 50 ℃ the strands are very brittle when they leave the extruder die (1.6 mm), at 60 ℃ the strands are very soft and show a tendency of adhesiveness to each other. All strands were cut manually into smaller pieces directly when leaving the die and spheronized at 600 rpm for 15 min. All tested pellets had similar shape characteristics and particle size distributions. Particle size should not have an effect on the release profiles tested. The resulting dissolution curves in Figure 47 show no impact of extrusion temperatures on SE S-370.

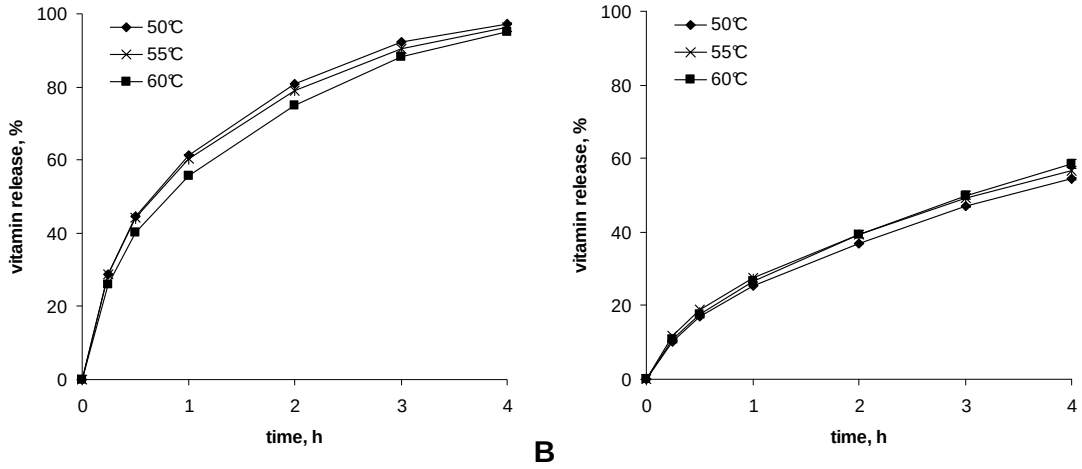


Figure 63. Release of pyridoxine (A) and riboflavin (B) from pellets obtained at different extrusion temperatures. Pellets contained 70 % SE S-370, 10 % PEG 4000, 15 % starch and 5 % vitamins (error bars are within the symbols)(for release of the other vitamins see Annex Figure 45A).

Within the temperature range where homogeneous strands were formed by the extruder no impact of temperature changes on the release profiles could be observed. The DSC curves (Chapter 3.1.2) showed quick recrystallisation when SEs are heated to the liquid crystalline state but not exceeding temperatures >90 ℃, or >80℃ for SE S-370. 50 ℃ was the only temperature where soft SE S-1170 strands could be produced. At 45 ℃ the extruder was completely blocked, at 55 ℃ sticky strands were produced which is why the test was not carried out for a SE S-1170 formulation. Within the extrusion temperatures no impact of temperature is expected.

Table 17. Diameter of the extrusion strands after extrusion at different conditions and cooling to room temperature. Die diameter: 1.5 mm

	Resulting diameter of strands, mm		
Extrusion temperature, ℃	**Screw speed 4 rpm**	**Screw speed 10 rpm**	**Screw speed 20 rpm**
50℃	1.77	2.13	n.a.
55℃	1.88	2.26	2.21
60℃	2.11	2.27	2.37

SE S-1170 was used to determine the impact of extrusion speed on the shape of the strands. It was observed before that SE S-1170 showed swelling of the strands during cooling. SE S-370 and S-770 showed only slight swelling. Pure SE S-1170 could be processed at 50 °C, 55 °C, 60 °C and at di fferent extrusion speeds to determine the diameter of the produced strands (die diameter: 1.5 mm) (Table 17). The strands were afterwards cooled down to room temperature. When leaving the die, no differences in diameter were observed. But when the strands cooled down to room temperature the strands swell and became solid (for images see Annex Figure 46A). With rising extrusion temperatures the strands extended their diameter to 118 - 141% of the initial die diameter. The reason of this phenomenon is not known. A theory is, that the SEs form a high ordered structure as seen in the LC studies and this structure needs more volume than is soft hot LC order. When additionally the screw speed, and therefore the shearing rate, was increased as well, the diameter reached an extension of 158 % of the initial die diameter. Usually extrusion is carried out at constant temperature and constant extrusion speed, a homogeneous formed product is expected from this continuous process. Knowing this especially in SE-1170 an alteration of speed should be avoided to assure narrow particle size distribution of the produced pellets.

6.1.7 Storage stability of sucrose ester-based pellets

To evaluate the shape stability of the SE matrices, pellets containing 80 % SE S-370, S-770 or S-1170, 15 % MCC and 5 % total vitamins were stored at 40 °C/75 % r.h. for 4 weeks in snap-on lid glasses. The low melting temperatures of the SEs can be a risk for shape stability of the pellets. The pellets were monitored optically and no change in pellet shape could be determined. Pellets, consisting of SE S-770 and S-1170 showed slight sticking to each other when they were removed from the climate chamber. Only slight agitation separated the pellets from each other. Due to the high viscosity of the liquid crystalline mesophase the shape of the pellets did not change even at high storage temperatures. SE S-370 is expected to be the most sensitive SE to heat because of the lowest clearing point (85 °C). All formulations showed constant loss on drying after 4 weeks at all tested climate conditions (LOD: ~1 %). The pellets showed no hygroscopicity therefore similar stability of the vitamins compared to melt granules samples is expected.

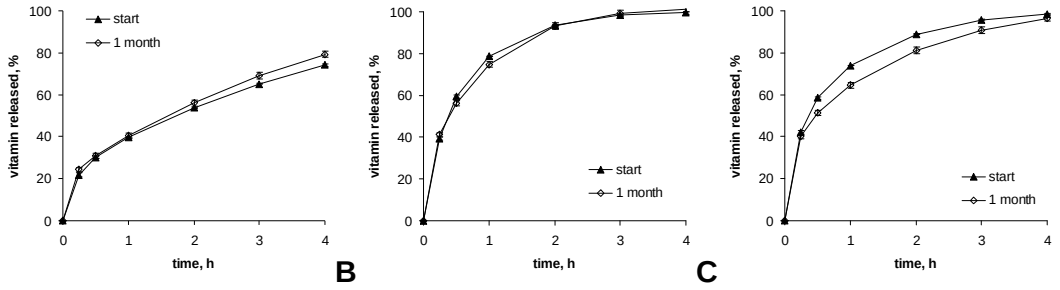


Figure 65. Release of nicotinamide from SE-based pellets after manufacturing and after 1 month storage at 40 °C/75 %r.h.. Pellets co ntained 80 % S-370 (A), S-770 (B) or S-1170 (C), 15 % MCC and 5 % total vitamins (nicotinamide, pyridoxine hydrochloride, riboflavin and thiamine nitrate). Error bars are within the symbols.

The tested batches, were additionally stored in PP containers at accelerated conditions, to test the release pattern of the pellets after storage for 4 weeks at 40 °C/75 % r.h.. In Figure 48 the release profiles from the different SE-based pellets are shown. Only slight changes within the normal variability were determined which showed again that SE-based matrices provide constant release profiles during short term stability studies. Again free flowing pellets remained after 4 weeks at humid conditions. The hot melt extrusion/spheronization process is suitable for the production of sustained release pellets. The release patterns of the pellets are not expected to change over storage time. Even for hot and humid conditions the results are very promising. Long term data for the products should be analysed.

6.2 Conclusion of pellet studies

The use of thermotropic liquid crystalline substances in pharmaceutical preparations produced by melt extrusion/spheronization process is little described in the literature. There are some investigations going on about liquid crystalline polymers of the use in pharmaceutics. SEs were shown to be applicable in melt extrusion technology. With their low melting ranges they are suitable for heat sensitive APIs. When extruding SE preparations it has to be taken into account, that they form liquid crystalline mesophases and have no classic glass transition. In liquid crystalline mesophases the order of the molecules is very high. Like in glass transition the material softens

what enables the molecules to change their order. They built highly ordered mesophases or later change their form to the isotropic cast. The SEs stay in one of the ordered states during softening. The isotropic state is only reached in the completely molten liquid. The isotropic liquid is reached at 85 ℃ for SE S-370 and >135 ℃ for SE S-770 and S-1170.

Homogeneous strands with non sticking surface could be produced through the extrusion of SEs. Subsequent pelletization of the extruded strands can increase the yield of the obtained pellets and improve the particle size distribution. Spheronization process could be adjusted by optimisation of spheronization speed and spheronization time. Spherically shaped pellets could be achieved with reduced abrasion in spheronization process through adjusting the content of spheronization aid and the choice of filler. The influence on the release profile using soluble and insoluble bulking agents could be shown. By alteration of the SE content, SE type and the choice of bulking agent a desired release profile over several hours can be achieved by melt extrusion/spheronization of SEs.

7 Sucrose ester-based tablets obtained by direct compression

For the development of sustained release tablets the behavior of matrix formers in direct compression is very important. Hydrogel matrices are commonly used in direct compression. To be competitive to these well-known substances new ingredients must show improved functionality and good processability. The easiest and most gentle way to manufacture tablets is direct compression. Production costs are very low and only a few parameters have an influence on the matrix behavior and APIs. Heat, humidity or oxidative processes are minimized when applying direct compression which is why very sensitive APIs can be processed through this method. To realize direct compression, raw materials have to show good flowing properties, compression behavior and form a homogeneous matrix to assure reproducible release profiles. As it was observed before, SEs have very bad flowing properties although it was investigated if other excipients can help to overcome this disadvantage which would offer one more field of application for SEs as sustained release matrix agents.

7.1 Experimental results and discussion

7.1.1 Dissolution profiles

Matrix forming agents are in general expensive excipients compared to MCC or magnesium stearate. Therefore the amount of matrix former should be as little as possible to achieve the desired sustaining effect. For the first study 10 % of SE S-370 was used as matrix former. 5 % was the total vitamin content of the four B-vitamins (nicotinamide, pyridoxine hydrochloride, riboflavin 5'-phosphate and thiamine chloride hydrochloride). A tablet weight of 500 mg and diameter of 11 mm was chosen as an applicable tablet size. The left space in the tablet which would usually be used for other vitamins was filled up with a mixture of povidone and different MCC grades.

In the first dissolution study a problem occurred what was later identified to be a general problem for direct compression of SEs. In Figure 49 a bend in the dissolution curve can be observed. After 30 min a sudden increase of vitamin content in the dissolution medium was determined. After completion of the dissolution it could be seen what happened to the tablet.

The NMR image in Figure 49 shows the appearance of capping during dissolution. In this picture only a thin layer on the surface of the tablet was separated from the tablet.

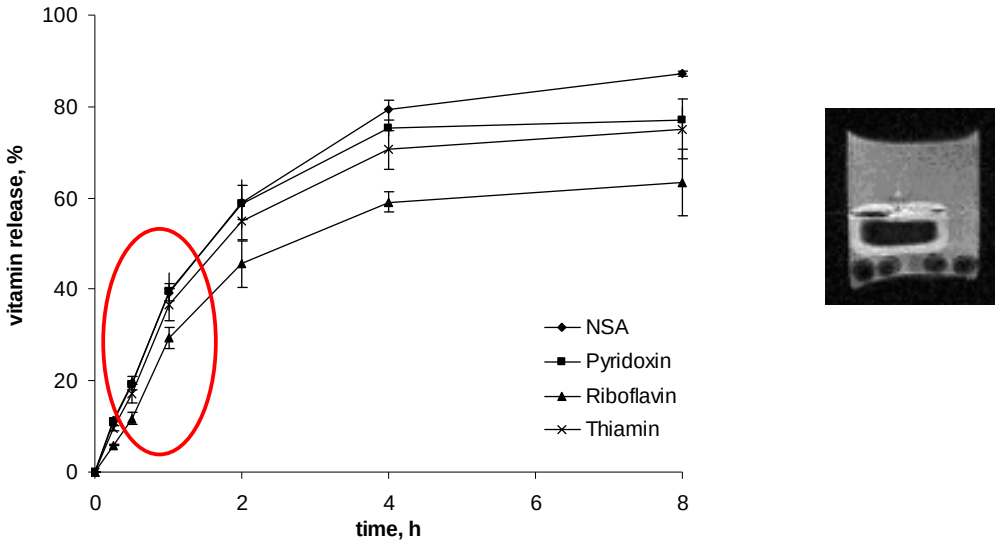


Figure 66. Bend in the dissolution curve due to capping (right: NMR images of the tested formulation). (Formulation: 10 % SE S-370, 5 % total vitamins, 80 % SMCC 50, 5 % Povidone)

In most cases the tablet was separated in two nearly equal sized parts as it is shown in Figure 52 (right). A higher contact surface to the dissolution medium leads to higher dissolution of vitamins and therefore a bend in the dissolution curve. Lipophilic and amphiphic SEs can also be used as lubricants. Their separating character predominates in the tested formulation. A matrix cannot be formed because of low binding within the tablet. But as it can be seen in the NMR image the lower part of the tablet, where no separation occurs, works very good as a matrix tablet. Therefore further studies should be carried out to overcome the capping problem. The effect of different excipients on the matrix formation and influence of the capping properties should be investigated.

In Figure 50 the NMR images of two formulations containing 10 % of SE S-370 as matrix former and 5 % total vitamin content of the four B-vitamins are shown. The tablet weight of 500 mg and diameter of 11 mm was the tested tablet size.

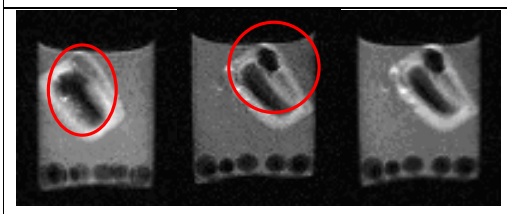
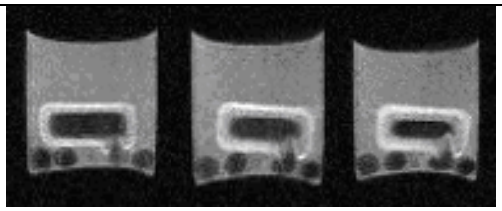
Formulation A Povidone : MCC PH200 65 : 35			Formulation B Povidone : SMCC 50 65 : 35		
					
50 min	70 min	90 min	50 min	70 min	90 min

Figure 67. NMR images after 50, 70 and 90 min. Tablets obtained by direct compression. (SE S-370 content 10 %, tablet weight 500 mg, diameter: 11mm.

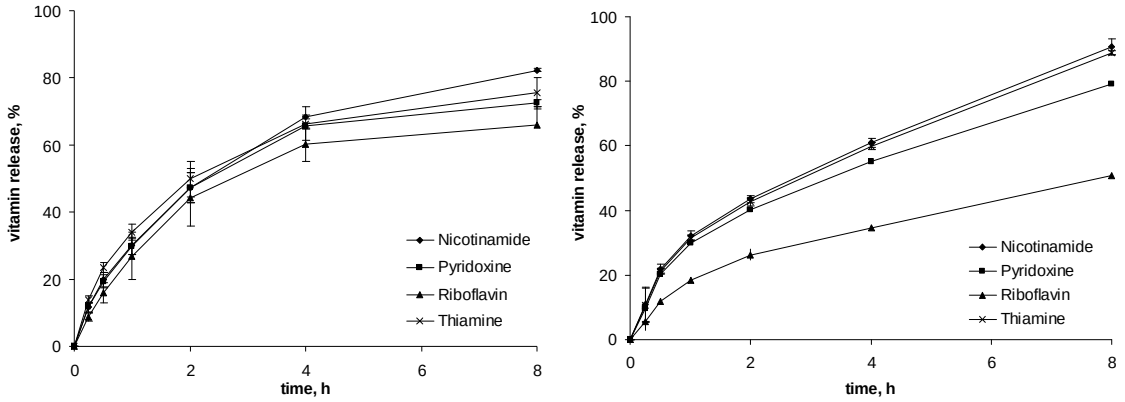


Figure 68. Simultaneous release of vitamins from tablets obtained by direct compression containing 10 % SE S-370, 5 % vitamins, 55 % povidone and 30 % MCC (A) or 30 % SMCC 50 (B). During dissolution studies capping occurred in both formulations.

MCC and povidone in a ratio of 65:35 was used as fillers altering the grade of MCC from Avicel PH 200 (Formulation A), a microcrystalline cellulose with an average particle size of 180 µm to SMCC 50 (Formulation B), a silicified microcrystalline cellulose with an average particle size of 60 µm. Formulation A swam in the dissolution medium (Figure 50). After 40 min the formation of an air bubble can be

observed and above this bubble the top of the tablet starts capping. In formulation B there is no air remained in the tablet therefore the tablet does not swim and shows no capping during the first 90 min which leads to a slower release of the vitamins compared to formulation A (Figure 51). After 14 h formulation B also shows capping (Annex Figure 47A). When this formulation is used for longer retardation it must be assured that no capping occurs while the dissolution of the active ingredients is not completed. In both dissolution curves the capping can not be seen because of the tested period of time. But when capping occurs the surface of the tablet will change during dissolution and a reproducible dissolution curve cannot be guaranteed. The point in time when capping occurs was found to be very much addicted to compression parameters and composition of the formulation.

7.1.2 Comparison of SE S-370 and S-770

SE S-370 is very lipophilic and forms a very waxy matrix which can cause this capping problem during dissolution. Therefore SE S-370 was exchanged by SE S-770 to determine differences in matrix characteristics. The tablet weight was lowered to 300 mg which leads to a SE content of 17 % and a vitamin content of 24 %. As filler a ratio of 60:40 Povidone and SMCC 90 was used. The samples were produced on an eccentric compression machine. The tablet characteristics were again very poor. With the highest immersion depth both formulations reached a hardness of only ~25 N which is very soft taking into account that the diameter of the tablet is 12 mm. Tablets were produced with two different immersion depth. In the softer tablets (17 – 23 N) air remained in the matrix structure which caused swimming of the tablets in water. When the tablet was compressed with a higher immersion depth the air was completely removed from the matrix and the tablet sank in water. The harder tablets were tested for their dissolution properties (Figure 52). SE S-770 performed slightly better than the lipophilic SE S-370. The lipophilic SE matrix is very hard and brittle. The amphiphilic SE forms a softer, flexible matrix. Both formulations again showed capping during dissolution. The NMR image below shows that capping occurred in the formulation containing SE S-370 after 8 h (Figure 52, right). It was seen before that capping can occur at different points in time. The formulation containing SE S-770 also showed capping.

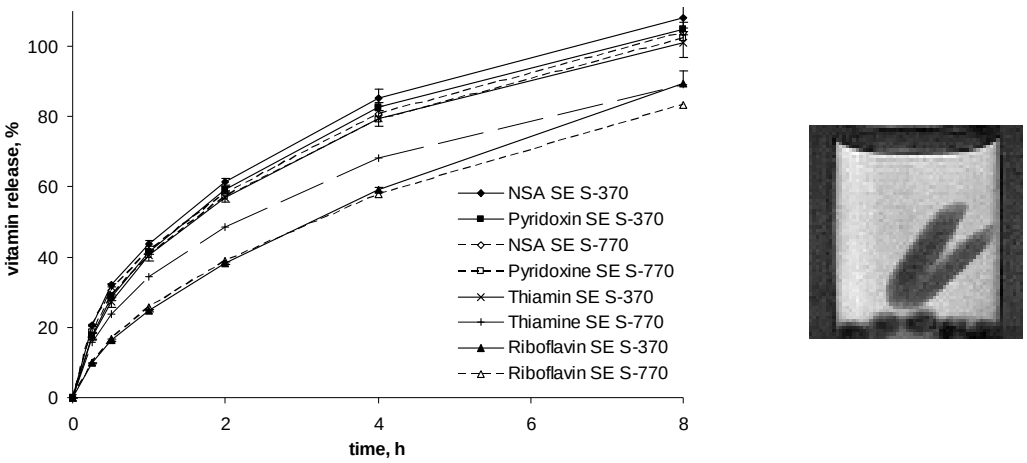


Figure 69. Left: Vitamin release from two formulations obtained through direct compression containing different SEs (SE content 17 %, total vitamin content 24 %, other excipients: Povidone:SMCC 90 60:40). Right: Tablet obtained by direct compression containing SE S-370 (17 %) after 8 h in phosphate buffer pH 6.8.

7.2 Conclusion of direct compression studies

The functionality of SEs as lubricants characterize the behavior in tablet formulations. Amphiphilic and lipophilic SEs have good separating characteristics. This separating effect seems to overbalance the matrix forming characteristics when SEs are used in direct compression. Concerning the release profile from the tablets good results were achieved from different formulations (for release curves of different compositions see Annex Figures 48 – 52A) but in all cases capping occurs at different time points. The hardness of the obtained tablets is too low for further handling. Bad flowing properties abet the incorporation of air in the tablets which causes capping during dissolution. Granulation in combination with substances showing high flowability and good binding characteristics can be a solution to obtain good flowing granules with better compressing characteristics. The amphiphilic SEs deserve more attention because their matrix forming behavior is much more promising than the matrix forming of SE S-370 in tablets. Risks and starting points for further investigations have been discovered. It was still not successful to release all vitamins homogeneously. An erodible matrix can be a solution to reach the dissolution of riboflavin in a similar profile as for the other vitamins.

8 Three layer tablet formulation with a controlled release layer

The results of the SE tablets obtained by direct compression were unsatisfying. The formulation of SEs in direct compressed tablets needs much more investigation before applying them in a nutritional product. Therefore other matrix formers have to be tested to enable the sustained release of multiple vitamins from a matrix tablet. HPC or HPMC offer a well-known controlled release system which probably can overcome the release problem of riboflavin through additional erosion of the dosage form. Quick/slow release systems are known in different designs of dosage forms [109,110]. For the development of a three layer tablet offering the advantage of immediate release as well as controlled release of vitamins over several hours these matrix formers were investigated. The sustained release layer should contain the vitamins thiamine (B_1), riboflavin (B_2), nicotinamide (B_3), pantothenic acid (B_5), pyridoxine (B_6) and ascorbic acid (C). The following vitamin salts were chosen as vitamin sources: thiamine chloride hydrochloride, riboflavin 5'-phosphate, nicotinamide, calcium pantothenate, pyridoxine hydrochloride and ascorbic acid. Probiotic bacteria were included in the formulation in a separated layer. In the immediately release layer minerals, fat-soluble vitamins or water-soluble vitamins with a resorption area in the duodenum can be added. The challenges of the development of such a nutritional product are the following:

- Limited weight of the complete tablet for consumer friendly application
- Limited weight of every tablet layer for optical reasons (homogeneous distribution of all layers)
- Defined tablet shape
- High load of active ingredients in every layer
- Homogeneous sustained release of the vitamins
- Assurance of the release profile of all vitamins
- Assurance of reproducibility of the system performance

The aim of the study was to develop a nutritional supplement which offers the controlled release of the defined B-vitamins over 6 - 8h in addition to immediately release of minerals, vitamins and probiotics. It should be investigated how triple

compression and the upon compressed second layer influence the performance of the sustained release matrix tablet. The tests of the three layer tablet formulation were first carried out as monolayer tablets. It was planned that the sustained release layer should be the first layer which is compressed in the three layer tableting process. The form of the tablets is therefore the same as in monolayer tablets. It is indicated in every study if mono- or three-layer tableting was carried out. The final shape of the tablet was not known in the beginning. All used tableting tools are indicated in the studies.

8.1 Experimental results and discussion

8.1.1 Comparison of different matrix formers

Five formulations were tested to get an impression of the effect of different matrix formers on the release patterns of pyridoxine in monolayer tablets. Considering the results of the earlier studies it is expected that the other vitamins are released in the same order as seen before and a prognosis of the release patterns of all vitamins can be made from the results of pyridoxine. Formulations containing HPMC, HPC, EC, glyceryl dipalmitostearate and glyceryl behenate with either tricalcium phosphate or microcrystalline cellulose (Avicel PH 200) as filling agents were obtained by direct compression. Tablet tools with a diameter of 9 mm and a curve radius of 13 mm were used. Tablets containing MCC and ethylcellulose, glyceryl dipalmitostearate and glyceryl behenate disintegrated in less than 12 min, therefore no dissolution studies were carried out for these samples. All other formulations were able to sustain the release of pyridoxine hydrochloride over 8 h (for release profiles see Annex Figure 53A). The formulations containing HPMC or HPC in combination with MCC gave the best results for an effective sustained release for pyridoxine. Both formulations were manufactured again with the combination of all vitamins the final product should contain. Again the four B-vitamins known from the SE studies (Thiamine, Riboflavin, Nicotinamide and Pyridoxine) were analysed. The release rates followed the same order known from the SE studies. In Figure 53 the hydration process of this HPMC tablet is shown.

30 min	60 min	120 min	150 min	180 min	240 min	360 min

Figure 70. NMR images of HPMC tablet containing 8 % HPMC K100M in phosphate buffer pH 2.7, flow through cell.

In the beginning the white area characterizes the gelling process in the outer regions of the tablets. High interaction of water and hydrogel former can be detected which forms a soft gel around the dry tablet core. After 2 h an inner white layer arises. The rubbery region between soft gel layer and inner white layer appears dark in the image. It is a region of stiff gel layer formation. The inner white layer could be identified as the hydrated region between the rubbery region and the dry tablet core. After 6 h only gel layer and rubbery region in the centre can be observed.

8.1.2 Variation of HPMC content

HPMC is known to reach a plateau for the maximum sustaining effect at a certain HPMC level. Therefore a study was started to figure out the optimum level of HPMC for a sustained release profile over 6 - 8 h. The used tablet tools were oblong shaped 10 x 18 mm. Again monolayers were investigated. In Figure 54 the release profile of nicotinamide at different HPMC levels is shown. No enhancement of the sustaining effect over 15 % HPMC content could be achieved. With a content of only 7.5 % HPMC the aim of release time over 6 - 8h could not be reached. Therefore a HPMC content of approximately 8 - 12 % is necessary to achieve the desired release profile.

The shape of the tablet can also have an influence of the release profile and the HPMC content has to be adjusted when the final tablets shape is determined. Compared to the shown release profile of nicotinamide, the dissolution rate of riboflavin 5'-phosphate is lower than of all other vitamins (See Annex 54A). But whereas the release rates of the other vitamins become slower during dissolution the release rate of riboflavin 5'-phosphate keeps nearly constant. This effect enables the incorporation of riboflavin 5'-phosphate into the formulation because of the constant release rate it can be assures that at the end of the dissolution period riboflavin is released completely from the system.

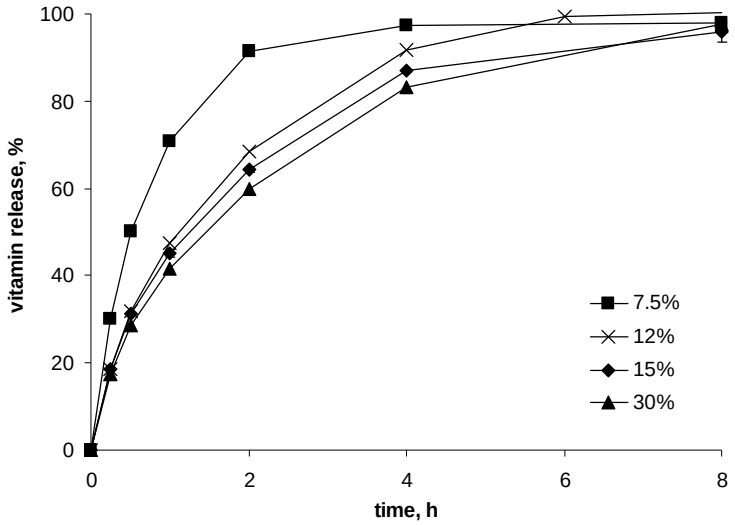


Figure 71. Release of nicotinamide from HPMC tablets containing different levels of HPMC K100M (Vitamins incorporated: nicotinamide, pyridoxine hydrochloride, thiamine chloride hydrochloride, riboflavin 5--phosphate, calcium pantothenate and ascorbic acid, other excipients: MCC PH 200, povidone, glyceryl dipalmito stearate)

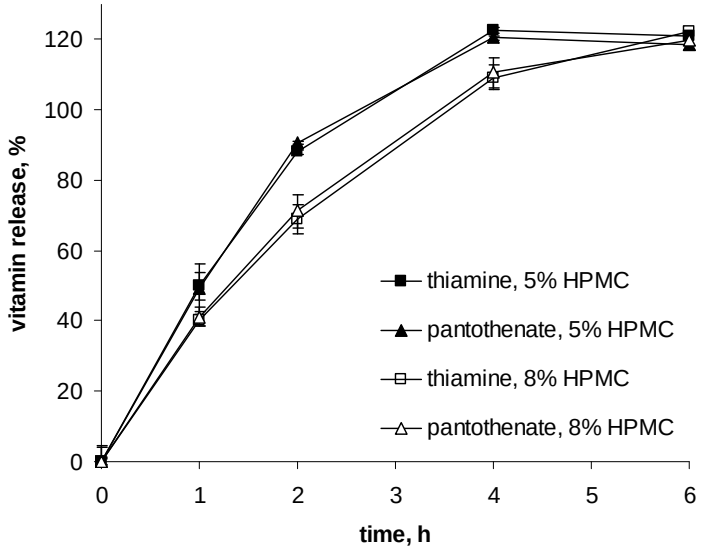


Figure 72. Release of thiamine and pantothenate from three layer tablets containing either 5 % or 8 % HPMC as matrix forming agent in the retard layer. Contents of more than 100 % are due to overdosages. For release of nicotinamide and pyridoxine see Annex Figure 55A)

The effect of HPMC content was also tested in a three layer tablet formulation. Formulations containing 5 % and 8 % HPMC were compressed into three layer tablets using tablet tools with oval shaped 8 x 18 mm which is the final shape of the tablet. Again an increasing sustaining effect can be observed between the two HPMC levels (Figure 55). But the sustaining effect in this tablet shape and as three-layer formulation is much lower compared to the previously investigated monolayers. After 2 h release the difference is the highest but after 4 h both formulations nearly reached the maximum release. The release curve from the three layer formulation is much steeper and the release is completed after 4 – 6 h. The reason for this effect is investigated in chapter 8.1.3.

8.1.3 Influence of compression parameters on the dissolution profile

Some hydrogel matrices in general are known for low impact of compression force onto the release formulation. But in this case, it has to be taken into account that three-layer compression is carried out and the release profile can alter under the triple compressing of the tablet with high main force of 1.5 – 2 t additionally, one side of the tablet is covered by the second layer compressed onto the sustained release tablet. Depending on the disintegration time of this second layer the hydrogel could be formed later because of delayed hydration.

Compression force studies were carried out with MCC as the second and third layer. To provide fast disintegration of the upper layers 2 % crosspovidon was added to the MCC. 1 % magnesium stearate was used as lubricant. This formulation disintegrated in ~ 1 min. The samples were compressed using the indicated compression forces in Table 18. The release curves of the single vitamins followed again the expected order of molecular weight and were distributed over a range of nearly 25 %. Riboflavin 5'-phosphate was again the slowest and nicotinamide the fastest released vitamin. Figure 56 shows the release curves of pyridoxine from the different samples. No difference in release due to compression force on the first layer or the main compression force on the tablet can be determined. The tableting process is now expected to very robust concerning the performance of the sustained release layer. Small variation in compression forces are not expected to affect the release profile.

Table 18. Compression forces on three layer tablets.

Force on 1st layer	Force on 2nd layer	Main force	Curve name
0.06 t	0.2 t	1.1 t	w - w
0.06 t	0.2 t	1.6 t	w - m
0.06 t	0.2 t	2.2 t	w - h
0.14 t	0.2 t	1.1 t	h - w
0.14 t	0.2 t	1.6 t	h - m
0.14 t	0.2 t	2.2 t	h - h

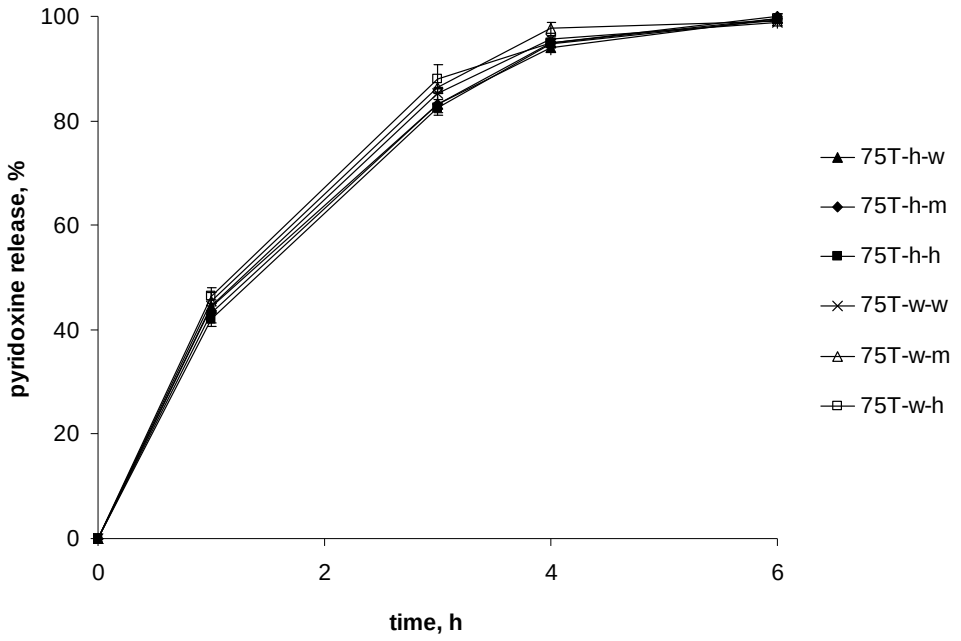


Figure 74. Release of pyridoxine from three layer tablets compressed with different compression forces. (For release of all other vitamins see Annex Figure 56A.) Tableting speed 75,000 tablets/h.

When fast disintegration occurs in the second layer the sustained release layer can swell like the previously tested monolayer and no alteration in the release profile can be determined (Figure 57). Under the same compression parameters another formulation was compressed onto the sustained release layer. This formulation had a disintegration time of ~ 60 minutes. In Figure 57 it can be observed that the release

in the beginning is delayed but the dissolution curves rises up much steeper than with the MCC formulation. The released amount of vitamins after 1 h was much lower than from the tablets where MCC was compressed on top. This occurs because of the smaller contact surface of the sustained release layer to the dissolution medium while the second layer dissolves over 1 h. In the formulation with MCC layer the disintegration is only 1 min therefore the whole surface of the sustained release layer is free for dissolution. Interestingly, after one hour the formulation with a disintegration time of ~ 60 min the release accelerates and reaches the same level of dissolved vitamins as the formulation with MCC.

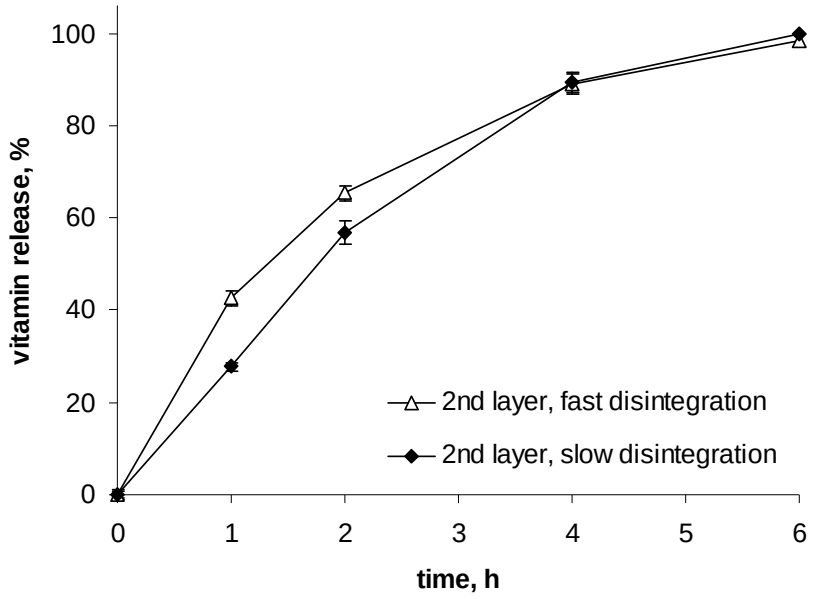


Figure 75. Release of ascorbic acid from three layer tablets containing 8 % HPMC. The second layer disintegrated within 1 min or within 60 min. (For the release of other vitamins see Annex Figure 57A)

This can be explained as follows. When the second layer dissolves slowly the gel can only be formed on three sides of the tablet. After the disintegration of the second layer the gel formation on this side starts but the gel formation on the other side is already further developed (Figure 58). This leads to a concentric positioned dry core in the middle of the matrix tablet. When now the gelling layer on the second side increases the dry tablet core will be reached earlier because of the shorter distance to the surface which leads to faster dissolution of the vitamins.

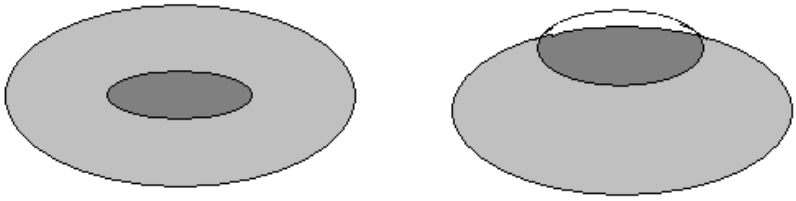


Figure 76. Schematic design of the swelling behaviour of the third HPMC-matrix-layer after disintegration of the first and second layer. Left: centric positioned dry tablet core after fast disintegration of second layer. Right: concentric positioned dry tablet core and rests of second layer on the controlling matrix layer.

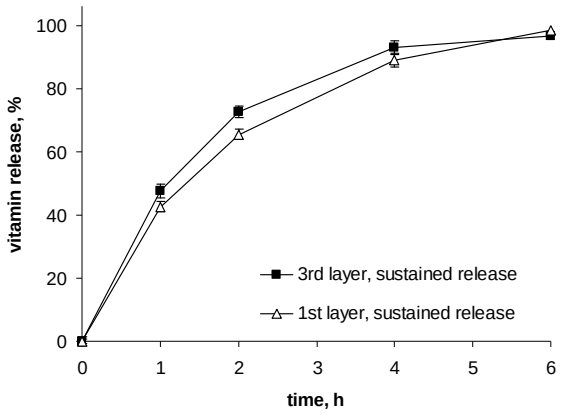


Figure 77. Release of ascorbic acid from three layer tablets containing 8 % HPMC. The sustained release layer is either compressed as first or third layer. The second layer compressed upon the matrix disintegrated in both cases within 1 min. For release of other vitamins see Annex Figure 58A).

The dissolution behavior of the vitamins when the sustained release layer is compressed as the first or the last tablet layer was investigated in another study. The shape of the different layers alters when it is compressed in a changed order. This can be another option to influence the release patterns of the vitamins. When the sustained release layer is compressed as the last layer the form is much thinner than when it is compressed as first layer. This leads to accelerated release of the vitamins

from the three-layer formulation, as expected (Figure 59). But astonishingly the difference is not very big. A difference in maximum ~ 10 % after 2 h occurs in the release curves. The total weight of the layer seems to be more dominant than the biconvex or convex form of the layer.

8.2 Conclusion of three layer formulation

With HPMC as matrix former it was possible to simultaneously control the release of 5 vitamins from the tablet. The release of all vitamins within 8 h could be assured. The vitamins nicotinamide, ascorbic acid, pantothenic acid, pyridoxine and thiamine showed simultaneous and homogeneous release profiles. Riboflavin which was the limiting factor in the SE studies could also be released in the desired period of time (Figure 60). But the release rate of the other vitamins could not be reached as it was seen in the SE studies. However, the erosion of the hydrogel system assures the complete release of the different sized vitamins. The disintegration time of the upon-compressed layer has much more impact on the release profile than the position of the sustained release layer within the tablet. When the layer is compressed as first or last layer the release curves do not change very much because of the constant layer weight. In three layer compression it has to taken into account that the disintegration time of the second layer can affect the gel formation of the sustained release layer. To achieve homogeneous gel swelling in the outer regions of the hydrogel layer fast disintegration of the second layer has to be assured. The disintegration time can also be used to alter the release profile, when non-disintegration layers are compressed upon the hydrogel tablet [111].

The formulation of a three layer tablet with sustained and immediately release patterns offer many options to alter the release of APIs. When only one API needs to be formulated the second and third layer can also be used to further design the release of the API [112,113]. Different levels of HPMC or other matrix formers can further influence the release and design a special release profile for an API.

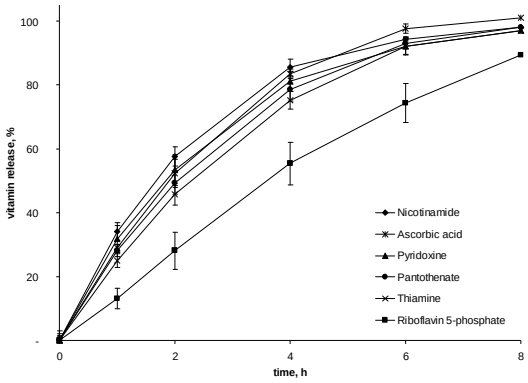


Figure 78. Release of vitamins from three layer tablets containing 15 % HPMC. The sustained release layer is compressed as first layer. The second and third layer compressed upon the matrix disintegrated both within 15 min.

9 Conclusion and perspective

The functionality of SEs can be used in a big variety of applications, as surfactants, stabilizers or solubility enhancers. There are many studies in progress in order to characterize SEs in their physico-chemical behavior or their application in novel technologies. These studies will generate much more information about SEs and will make their use in pharmaceutical application much safer. Publications about SEs in the last five years showed the wide variety of investigation and use of SEs in different scientific fields. However, the field of solid dosage forms as one application for SEs has been rarely investigated in the past.

SEs are very promising pharmaceutical excipients also for the use in solid dosage forms. Their application in different dosage forms prepared by different manufacturing methods could have been shown and makes them very interesting for the development of new pharmaceutical products. In this thesis the use of SEs in granulation, tableting and hot melt extrusion is described. It could be shown that it is possible to formulate vitamins in SE-based solid dosage forms with sustained release patterns.

The variety of SE types makes them on one hand difficult to characterize in general but on the other hand it also offers a choice of excipients fitting perfect in whichever application is needed. There are raw materials on the market containing different kinds of fatty acids e.g. sucrose laurate, oleate, palmitate and stearate or different numbers of fatty acid esters per sucrose molecule. They can alter from mono- to pentaester. In this thesis SE stearates were tested for their application in different solid dosage forms to get good comparison of the different formulations. It could have been shown that the wide range of HLB values offers a fantastic tool to adjust release rates depending on the physico-chemical properties of the API used.

The research on these systems showed the advantages but also the risks in the use of SEs in pharmaceutical application. However, the advantages prevail over the risks by far. One drawback discovered in the studies of this thesis was limited to the difficulties in handling of the powder. Staff has to be protected from the fine dust which arises due to the very small particle size of the powder. SEs also have good foaming abilities which can make cleaning of manufacturing devices quite complicated because of great amounts of foam formed during the cleaning process.

The application of SEs in tablets especially in direct compression was found to have its boundaries. The lubricant character of all SEs avoids the formation of binding forces within the tablet. The combination of different excipients can help to improve binding in the tablets but should not prevent matrix formation of the SE. The release curves of the tablets show very promising results. But the capping problem bears the risk of dose dumping when applied in humans which is not acceptable.

Many SEs are also available in pharmaceutical grade. SEs have approval for food use without any limitation of quantity. The only limitation for food use is the content of ≥ 70 % mono- and diesters in the substance. However, SEs did not reach GRAS status yet [114]. The toxicity for oral use was investigated by Yoshida et al. and Takeda et al. in rats and found not to be chronically toxic or carcinogenic [115,116]. No harmful effects are expected from the oral use of SEs.

The advantage of the wide variety of SE types was discussed before. Astonishingly, also the methods of manufacturing reached from wet granulation over compression to hot melt technologies. Depending on the physico-chemical properties of the vitamins every method can be used to produce sustained release formulations. In conclusion of this thesis the following effects were observed in all SE-based formulations:

It could have been shown that the order of release of the vitamins nicotinamide – pyridoxine – thiamine – riboflavin followed the ranking of their molecular size 122.13 Da, 170.18 Da, 265.5 Da or 376.37 Da (molecular size of the dissociated ion). But an altered water solubility can also influence the release rate to a small extend. It was shown that there was a difference in the diffusion coefficients of thiamine nitrate and thiamine chloride hydrochloride or riboflavin and riboflavin 5'-phosphate altered in dependence to their water solubility. The diffusion coefficients rise from thiamine cation in the case of thiamine nitrate, thiamine cation in the case of thiamine chloride hydrochloride and from riboflavin to riboflavin 5'-phosphate. Molecular size and water solubility must be considered when choosing the SE for the formulation.

The particle size of the system nevertheless is important for the period of release time. In granules and pellets the release could be sustained over 4 – 6 h, in tablets it could be sustained up to 8 hours and more depending on the physico-chemical properties of the vitamins. The period of release is regulated by the size and water

solubility of the vitamins. Riboflavin could be controlled much easier over a longer period than the very good soluble vitamins.

Furthermore, the manufacturing method influences the release patterns and the release mechanism to a big extend. Wet granulation was able to sustain the release of big sized poorly soluble riboflavin molecules. Many formulations using wet granulation disintegrated partially and where therefore simultaneously diffusion and erosion controlled. Compression sustained the release very well. In all cases of compressed granules the release mechanism was diffusion controlled even when they were compressed into mini tablets. When melt granulation was applied the release mechanism changed from diffusion controlled to nearly zero order like release in mini tablets or even in pellets. Melt extrusion was found to be the most effective way to embed vitamins in the matrix and control their release. In hot melt extrusion the release rate of riboflavin was very low despite the small diameter of the particles.

In all cases the concentration of SE in the formulation and the type of used SE determine the degree of retardation of the vitamins. For hot melt extrusion it was possible to use pure SE matrix with dispersed vitamins without any further additives. A content of 20 % SE in the formulation resulted in high erosion of the dosage form, but a content 50 – 100 % was found to build a good and stable matrix system. The use of different excipients also influenced the release profile. Soluble or hydrophilic substances as glucose increased the release rate, insoluble or hydrophobic substances as ethylcellulose could further extend the release in all cases tested.

In matrix mini tablets the reason for different release profiles from the different SE types could be shown. The matrix forming mechanism of the SE types altered with an increasing HLB value. Swelling behavior and water penetration velocity into the tablets determined the release patterns of the matrix system. Diffusion played a role in all formulations, but in the case of mini tablets additional effects through swelling and water penetration velocity could be detected. The hydrophilic SE S-1170 showed reduced water penetration due to distinctive swelling behavior. In comparison to HPMC or HPC matrices no formation of gel structures or rubbery regions in the matrix could be detected.

Pellets were one very promising option for the application of SE matrices and yet very little data is published. Pellet formulations containing SEs as matrix forming

agents could be used to sustain the release of the tested vitamins over 4 – 6 h. Again the different hydrophilicity of the SEs determined the release profile from pellet formulations. The hot melt twin screw extrusion of thermotropic liquid crystalline carbohydrate amphiphils for pharmaceutical applications has not been described in the literature yet. The application of SEs in this technology did not cause any difficulties and the period of release could even be extended compared to the melt granules. The optimization of the extrusion/spheronization process did only belong to yield, shape or process parameters. Due to their functionality as lubricants no further additives were needed.

The stability tests for the different applications were also very promising but long term stability data should be produced to assure stability of the vitamins and constant performance of the dosage forms during the shelf life of the product. The amphiphilic structure of the substance protected the vitamins which are sensitive to humidity especially in compacting or melt technology. The uptake of water into the systems is very low during storage even under very humid climate conditions. For sensitive APIs the matrix of SEs could increase the stability of the actives. If no sustained release is needed, depending on the properties of the API a hydrophilic SE can be used to protect the API but not to control the release.

The development of a three layer formulation showed that the order of release of the vitamins from the hydrogel system is similar to the release from SEs. Knowing the release of one vitamin, the release of the other vitamins will follow the expected order. This knowledge can reduce analytical effort to a minimum. In preformulation studies only single vitamins can be analyzed to find the desired release profile. Molecular mass and water solubility can be used to classify the vitamins or APIs in a ranking order.

The use of thermotropic liquid crystalline substances in pharmaceutical application is not investigated very much. Lately there have been some studies on liquid crystalline polymer application. The phenomenon of liquid crystalline behavior and its impact on the release mechanism could be very interesting in the development of new dosage forms. The mechanism of matrix formation in hot melt technologies through the existence of thermotropic liquid crystalline mesophases could not yet be described in more detail. The mechanism of release is expected to be determined by the lyotropic formation of the SEs within the tablet. The formation of thermotropic LC mesophases

can bear the chance to formulate APIs which are not yet accessible. The cholesteric, foam-like mesophase of the amphiphilic types could be an interesting field of investigation in the future. The very high surface of the structure could increase solubility of APIs. The information from technical applications of liquid crystals can be used to enable the development of innovative controllable dosage forms.

This study discussed the application of SEs in different solid dosage forms. It showed their wide variety of application for controlled release matrices. Matrix forming mechanism, release patterns and release mechanism were discovered using different techniques. This work closes the gap between the knowledge about the use of SEs as controlled release matrices and showed a very promising alternative to hydrogel matrices.

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List of publications

Oral presentations

T. Seidenberger, H. Bley, F. Siepmann, H.Metz, J.Siepmann, K. Mäder, Characterisation of SE matrices using benchtop NMR, CRS local chapter, Halle, Germany (2009).

Poster presentations

T. Seidenberger, H. Bley, F. Siepmann, J.Siepmann, K.Mäder, Simultaneous and controlled release of multiple vitamins, 6th World meeting on Pharmaceutics, Biopharmaceutics and pharmaceutical Technology, Barcelona, Spain (2008).

T. Seidenberger, H. Bley, F. Siepmann, J.Siepmann, K.Mäder, Simultaneous controlled release of multiple vitamins from SE-based tablets: How the SE type and content determine the release mechanisms, Annual meeting of the AAPS, Atlanta, USA (2008).

T. Seidenberger, H. Bley, F. Siepmann, K.Mäder, J.Siepmann, Sucrose esters in melt extrusion and spheronization processes, 7th World meeting on Pharmaceutics, Biopharmaceutics and pharmaceutical Technology, Valetta, Malta (2010).

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Erklärung

Hiermit erkläre ich gemäß § 5 (2) der Promotionsordnung der Mathematisch-Naturwissenschaftlich-Technischen Fakultät der Martin-Luther-Universität Halle-Wittenberg, dass ich die Ergebnisse der vorliegenden Dissertationsarbeit

Sucrose ester stearates,
amphiphilic matrix systems for the formulation of
sustained release preparations

am Institut für Pharmazeutische Technologie und Biopharmazie der Martin-Luther-Universität Halle-Wittenberg unter Anleitung von Herrn Prof. Dr. Karsten Mäder selbständig erarbeitet bzw. im Rahmen der angegebenen Kooperationen erhalten habe und nur die in der Dissertation angegebenen Literaturstellen und Hilfsmittel verwendet habe.

Weiterhin habe ich diese Arbeit bisher an keiner in- oder ausländischen Fakultät als Dissertationsschrift vorgelegt.

Halle (Saale), den

Tanja Seidenberger

Annex

Vitamins	sensitive to				
	acid	base	O_2	UV	heat
Thiamine		x	x		x
Riboflavin		x		x	x
Nicotinamide					
Pyridoxine				x	x
Pantothenic acid	x	x			x
Ascorbic acid		x	x	x	x

Figure 1.A: Sensitivity of vitamins to environmental influences.

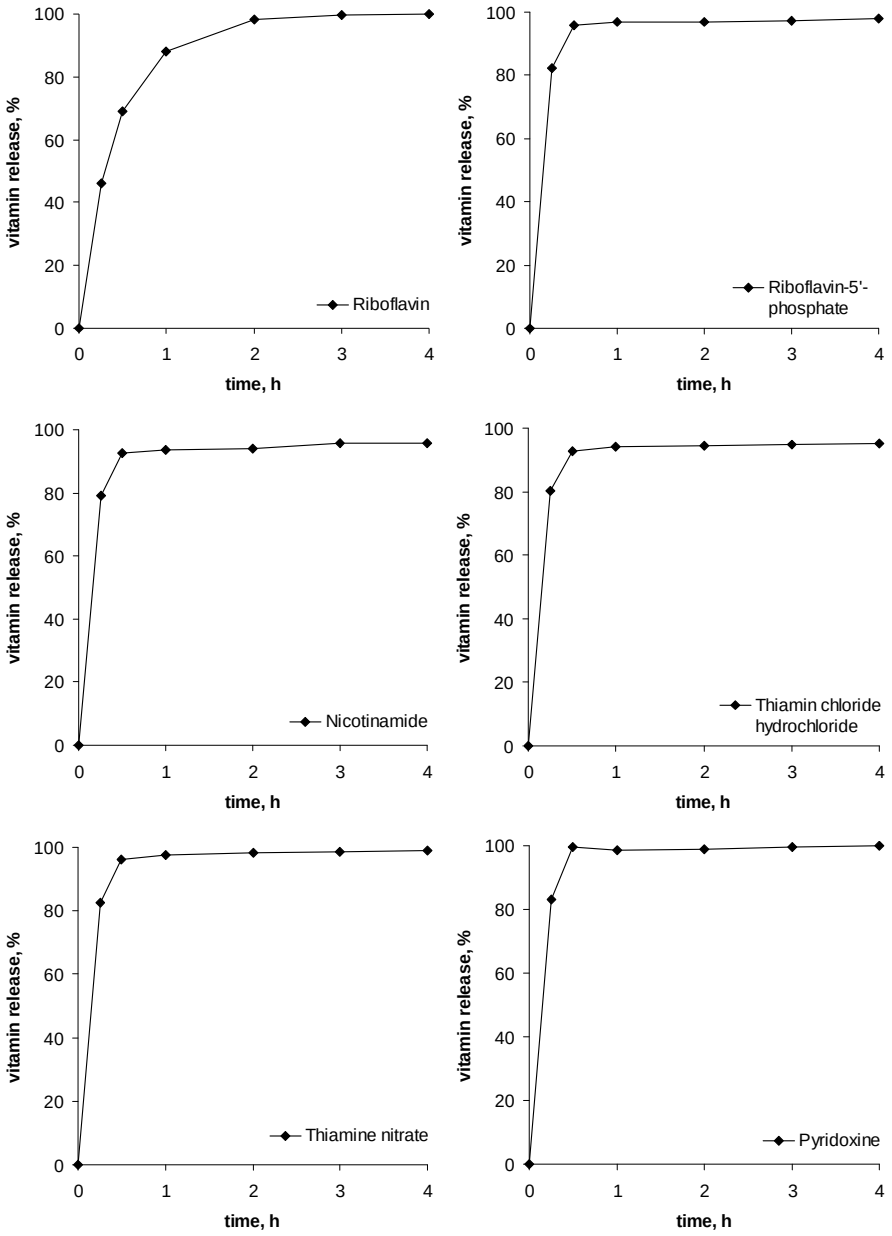


Figure 2.A. Dissolution of the used vitamins (n=1) in phosphate buffer.

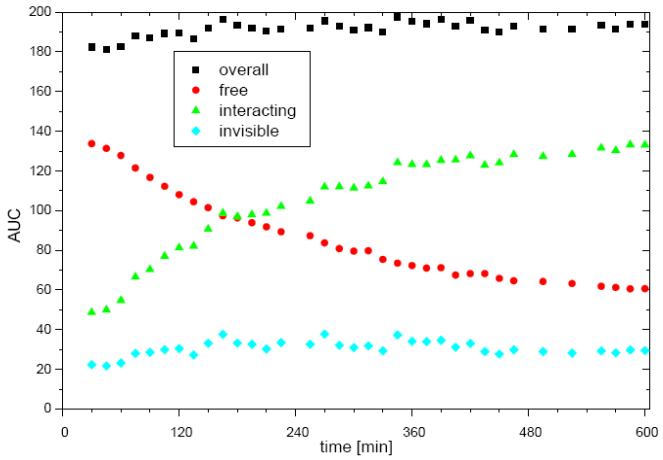


Figure 3.A. Increase or decrease of the AUC of interacting or free water molecules in a HPC tablet sample.

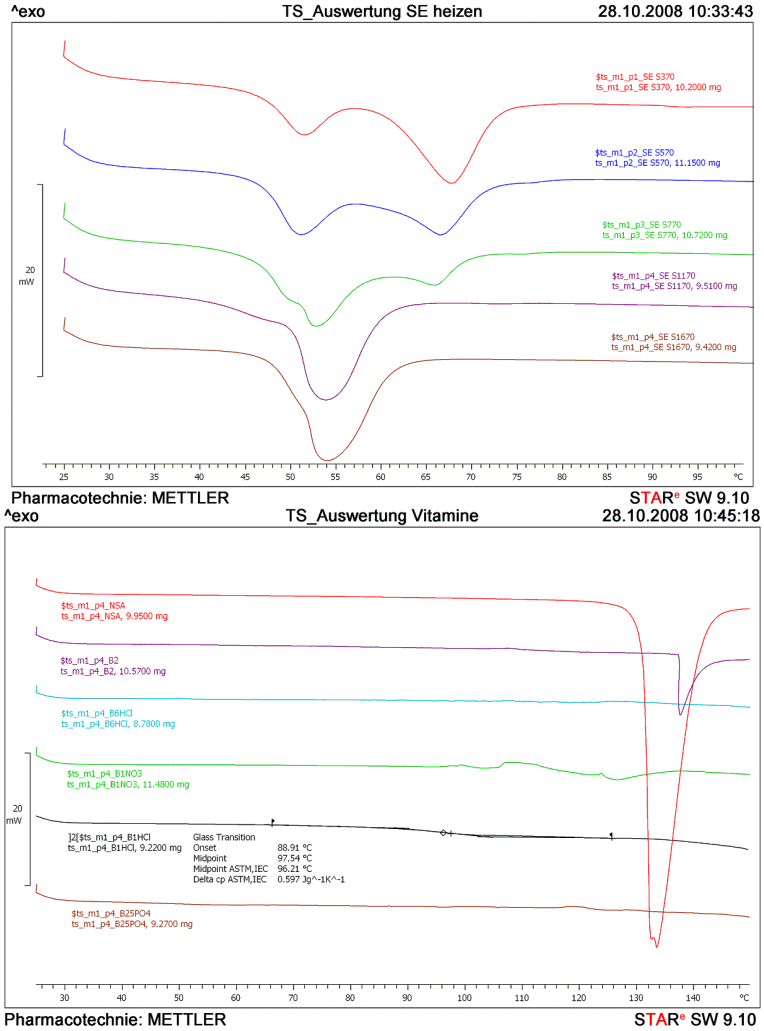


Figure 4.A. DSC heating curves from 25 ℃ to 150 ℃ of pure SEs (from up to down: S-370, S-570, S-770, S-1170, S-1670) and the vitamins nicotinamide, riboflavin, pyridoxine hydrochloride, thiamine nitrate, thiamine hydrochloride and riboflavin-5'-phosphate.

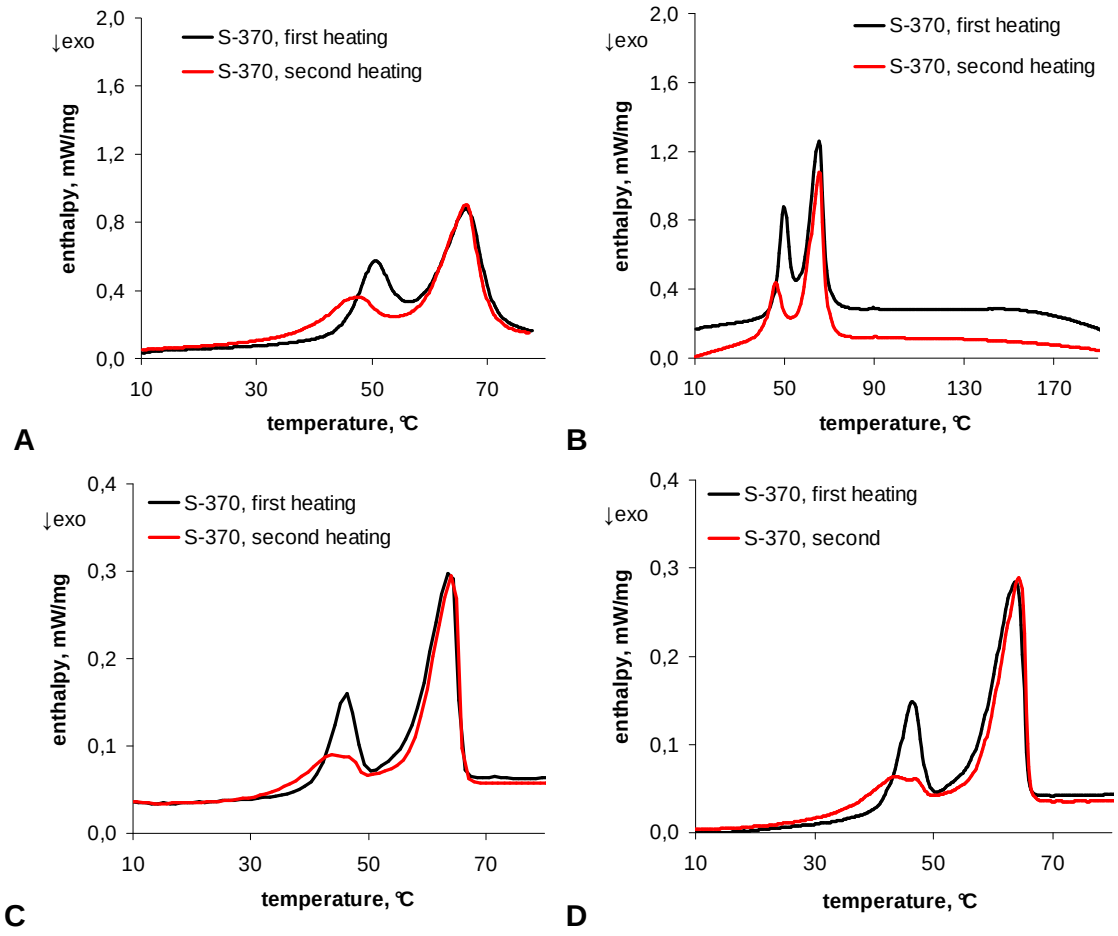


Figure 5.A. DCS measurements of SE S-370. (A) heating rate: 10 K/min, to 80 ℃, (B) heating rate: 10 K/min, to 200 ℃, (C) heating rate: 2 K/min, to 90 ℃.

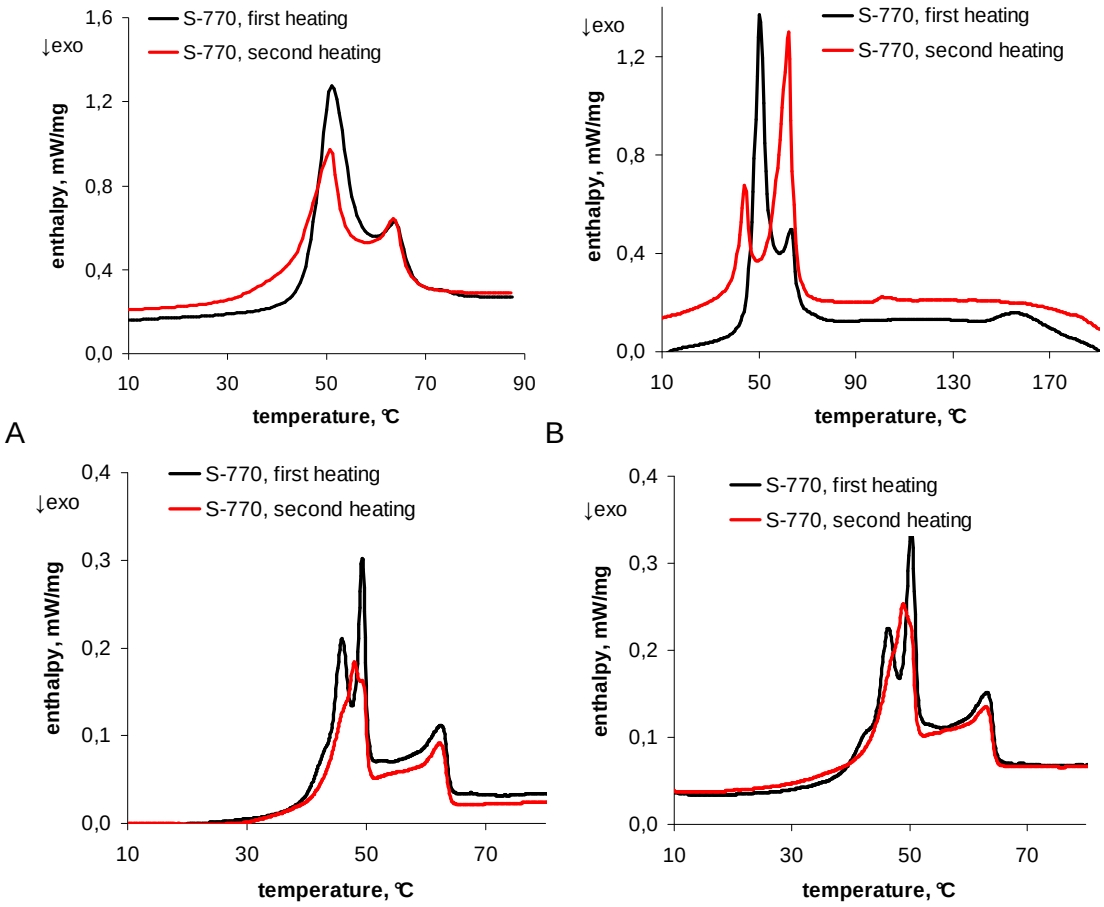


Figure 6.A. DCS measurements of SE S-770. (A) heating rate: 10 K/min, to 80 ℃, (B) heating rate: 10 K/min, to 200 ℃, (C) heating rate: 2 K/min, to 90 ℃.

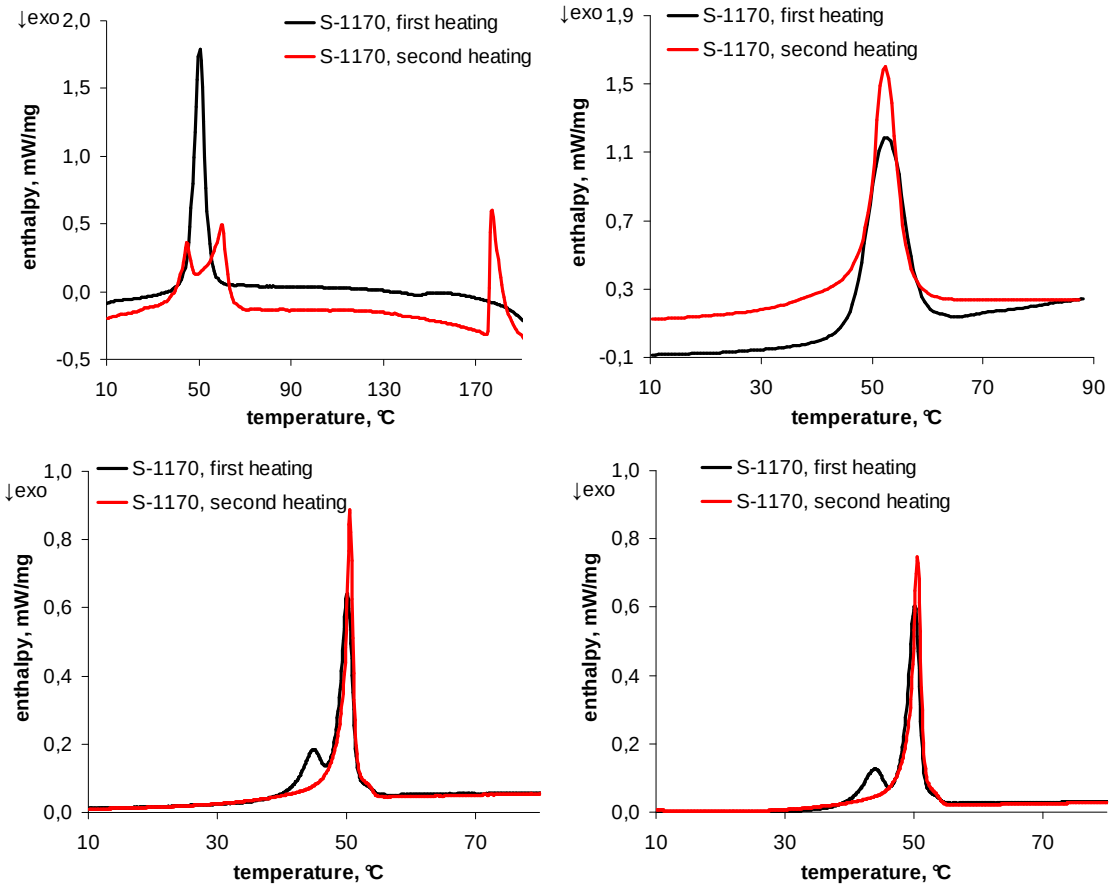


Figure 7.A. DCS measurements of SE S-1170. (A) heating rate: 10 K/min, to 80 ℃, (B) heating rate: 10 K/min, to 200 ℃, (C) heating rate: 2 K/min, to 90 ℃.

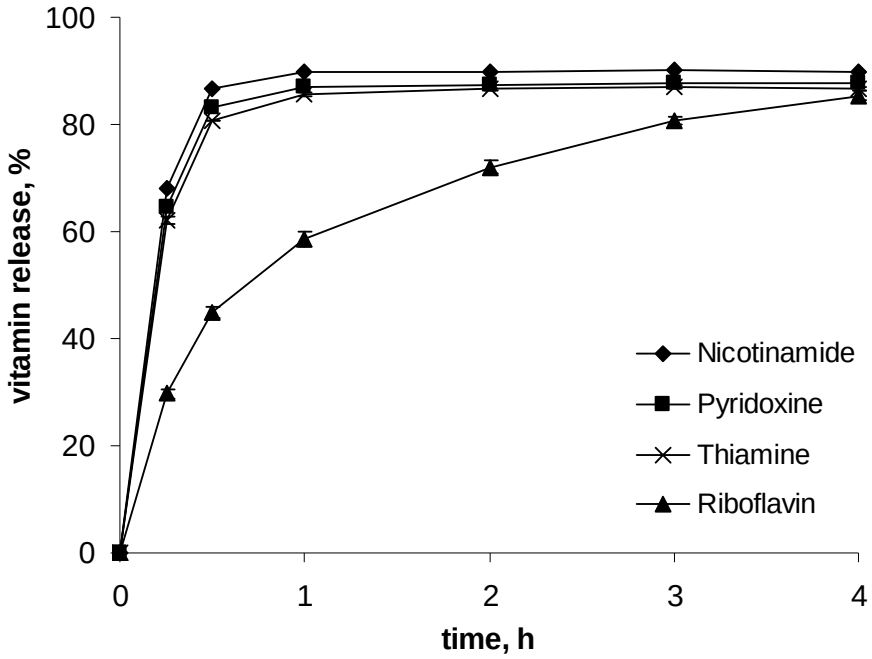
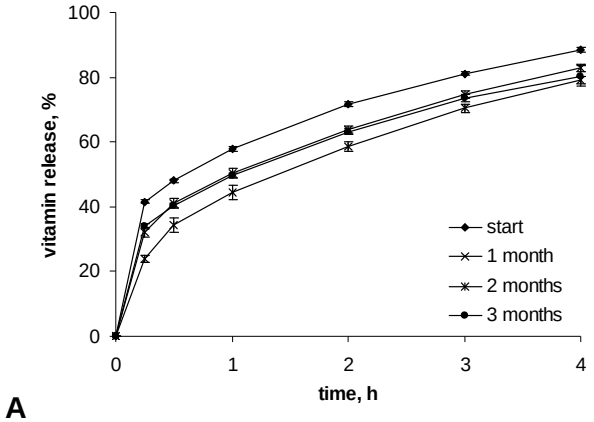


Figure 8.A. Release of vitamins from granules obtained by wet granulation containing 80 % SE S -370, 15 % MCC and 5 % vitamins. The granules disintegrate during dissolution therefore no diffusion coefficients were determined.



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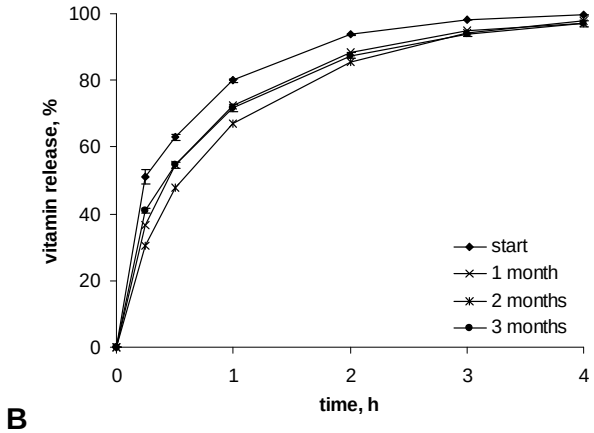

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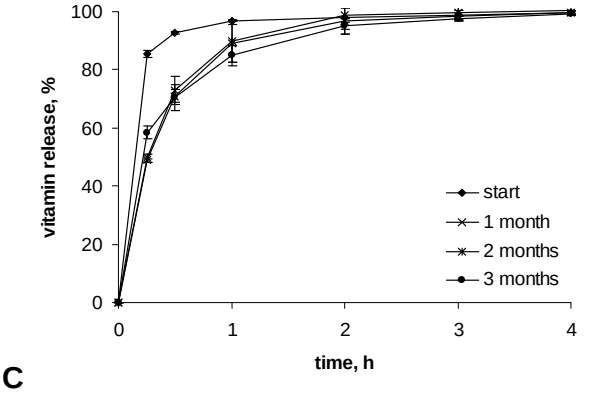
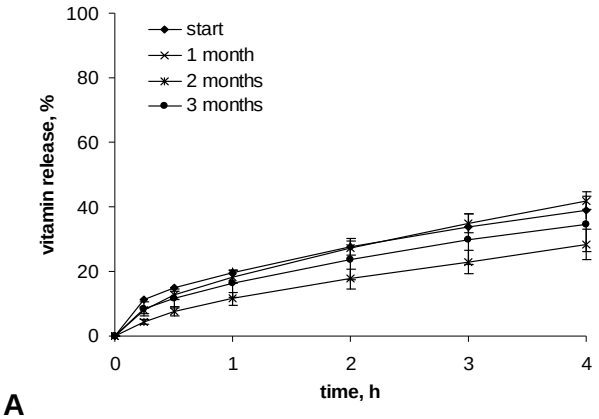


C ?

Figure 9.A. Nicotinamide release from granules stored in PP containers for 6 month obtained by melt granulation (A), wet granulation (B) and compression (C). (80% SE S-370, 5% total vitamins and 15% MCC)



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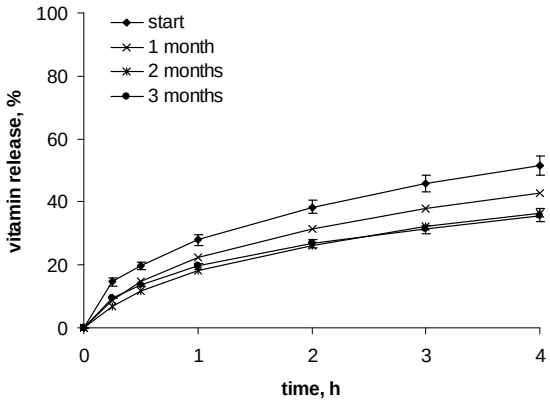

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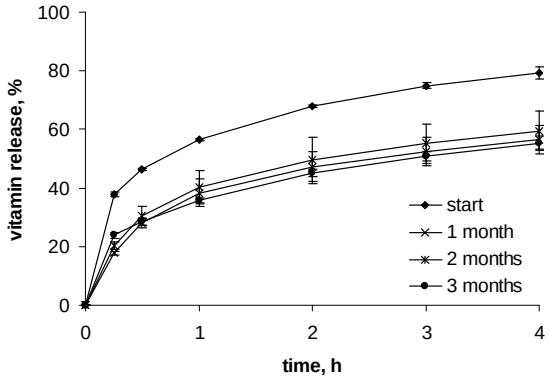
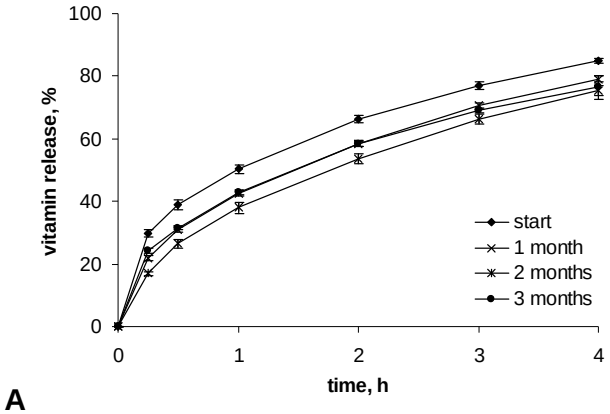


C

Figure 10.A. Riboflavin release from granules stored in PP containers for 6 month obtained by melt granulation (A), wet granulation (B) and compression (C). (80% SE S-370, 5% total vitamins and 15% MCC)



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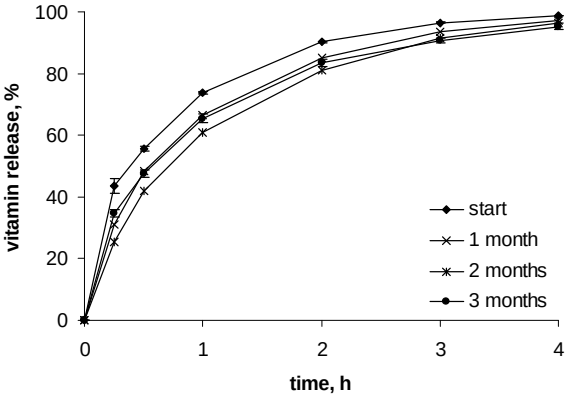

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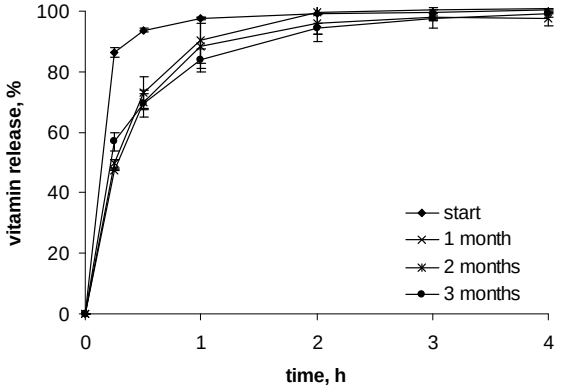


C

Figure 11.A. Pyridoxine release from granules stored in PP containers for 6 month obtained by melt granulation (A), wet granulation (B) and compression (C). (80% SE S-370, 5% total vitamins and 15% MCC)

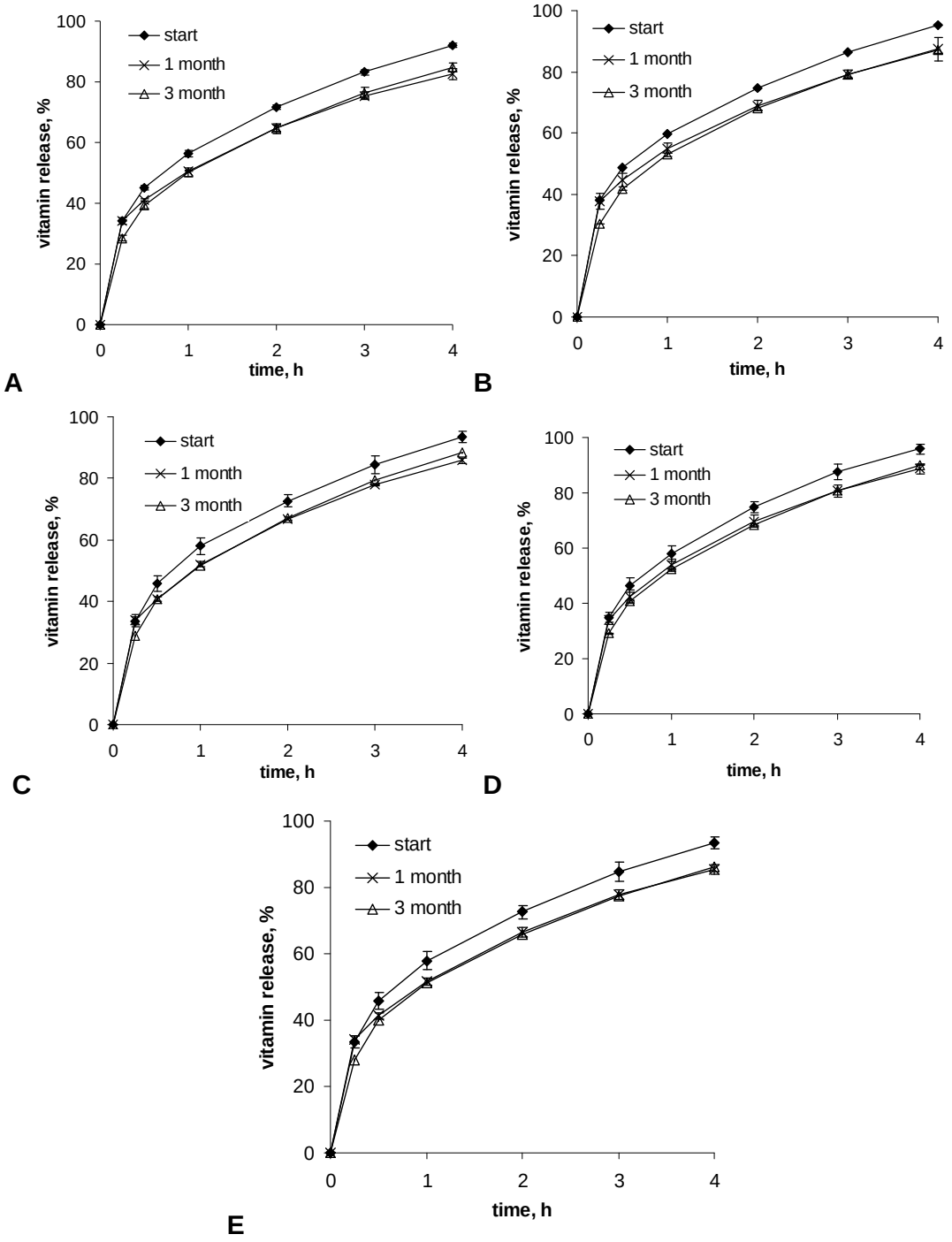


Figure 12.A. Nicotinamide release from granules obtained by melt granulation stored for 3 month in PP containers (80% SE S-370, 5% total vitamins and 15% MCC) at different conditions (A: 24h, 40℃, afterwards 25℃ / 60% r.h.; B:24h, 30℃, afterwards 25℃/ 60% r.h.; C: 24h, 8℃, afterwards 25℃/ 60% r.h., D:24h, -18℃, afterwards 25℃/ 60% r.h.; E: stored at 8℃)

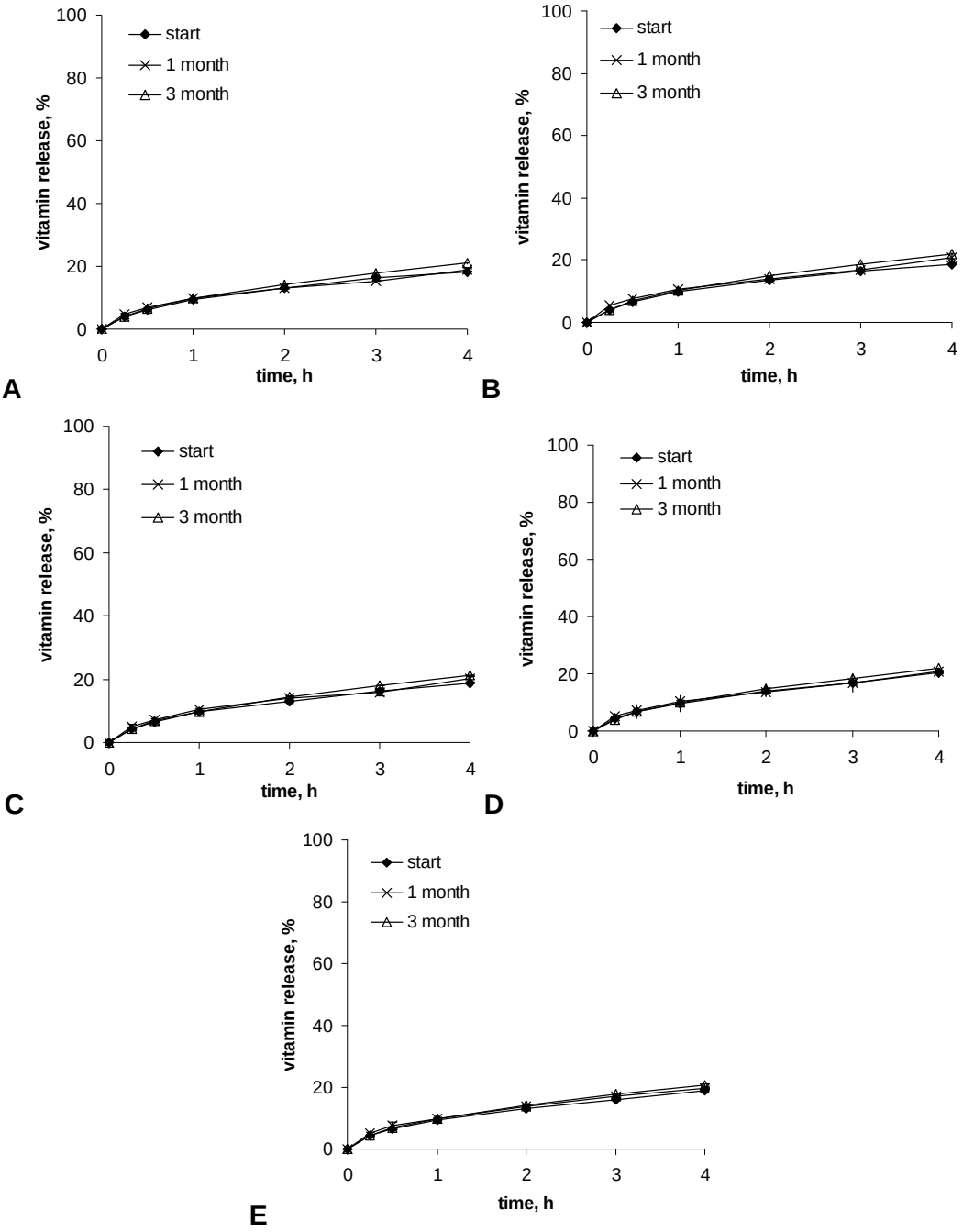


Figure 13.A. Riboflavin release from granules obtained by melt granulation stored for 3 month in PP containers (80% SE S-370, 5% total vitamins and 15% MCC) at different conditions (A: 24h, 40℃, afterwards 25℃ / 60% r.h.; B:24h, 30℃, afterwards 25℃/ 60% r.h.; C: 24h, 8℃, afterwards 25℃/ 60% r.h., D:24h, -18℃, afterwards 25℃/ 60% r.h.; E: stored at 8℃)

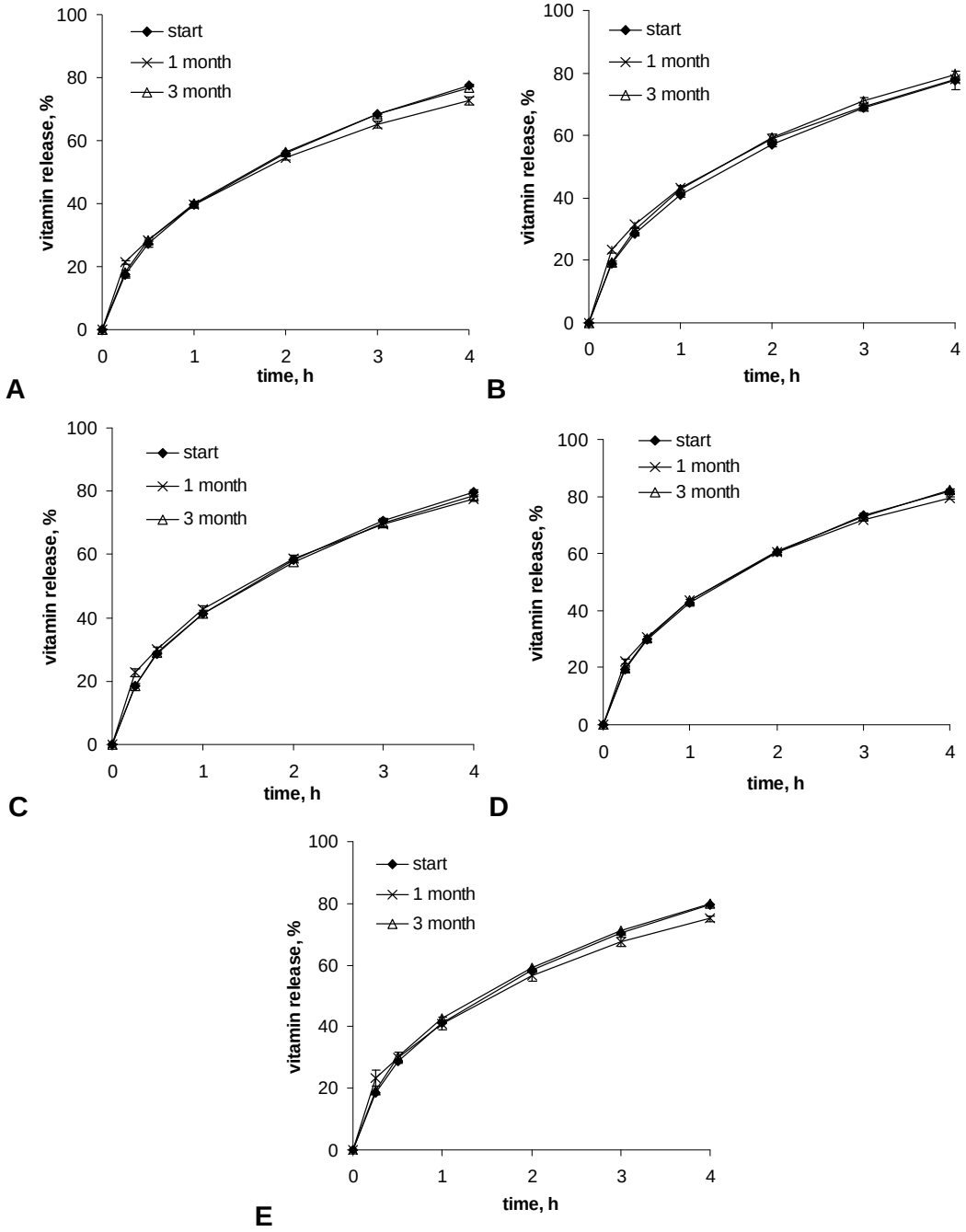


Figure 14.A. Pyridoxine release from granules obtained by melt granulation stored for 3 month in PP containers (80% SE S-370, 5% total vitamins and 15% MCC) at different conditions (A: 24h, 40℃, afterwards 25℃ / 60% r.h.; B:24h, 30℃, afterwards 25℃/ 60% r.h.; C: 24h, 8℃, afterwards 25℃/ 60% r.h., D:24h, -18℃, afterwards 25℃/ 60% r.h.; E: stored at 8℃)

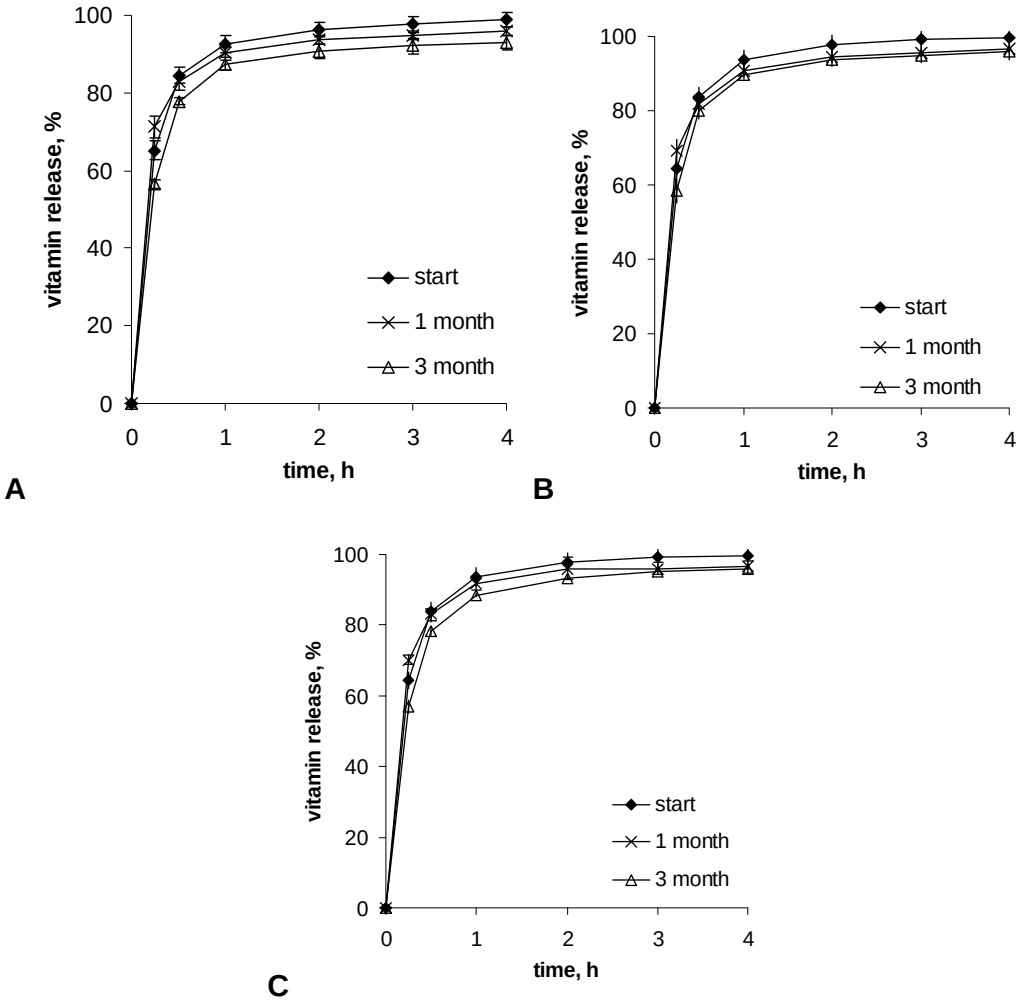


Figure 15.A. Nicotinamide release from granules obtained by wet granulation stored for 3 month at 25℃/60r.h.. In CSP vial, LOD 2.8% (A); with additional drying in CSP vial; LOD 1.2%, with additional drying in PP containers, LOD 1.2%. (80% SE S-370, 5% total vitamins and 15% MCC)

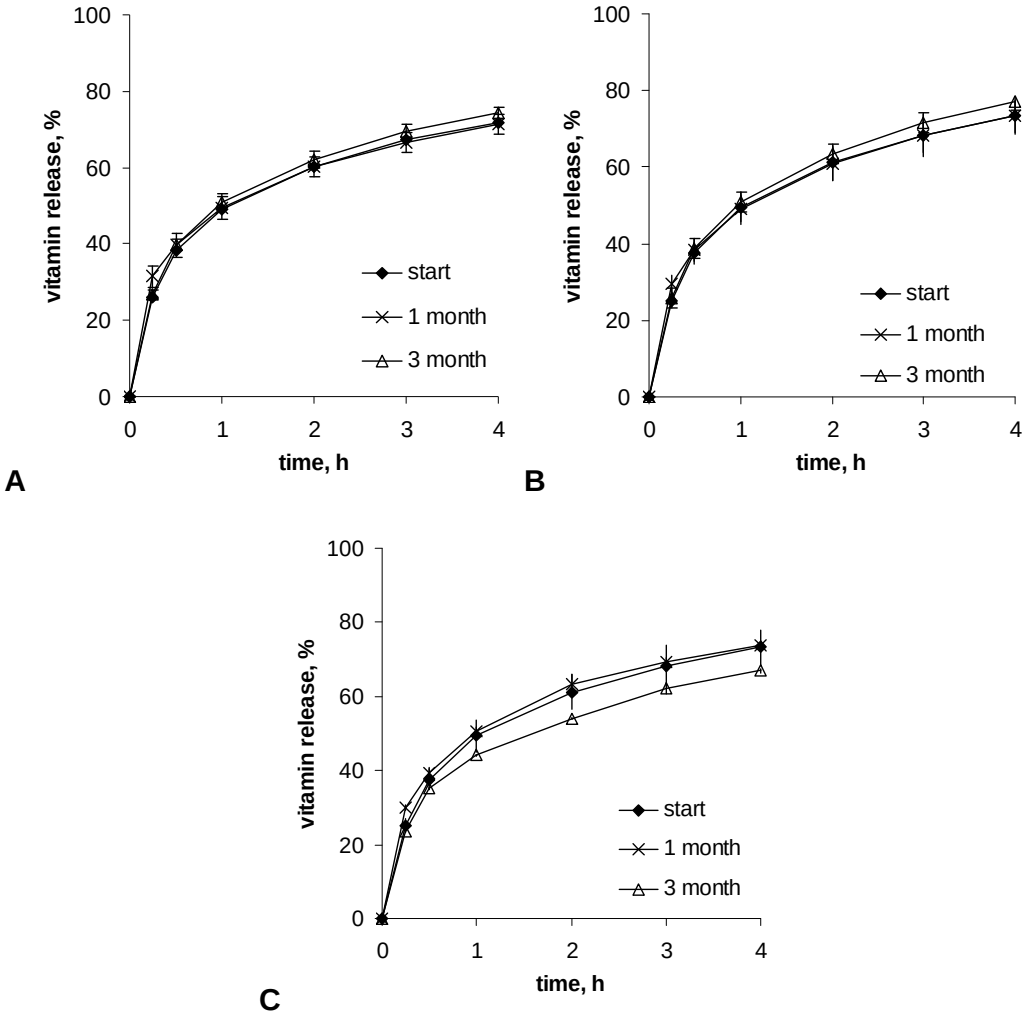


Figure 16.A. Riboflavin release from granules obtained by wet granulation stored for 3 month at 25℃/60r.h.. In CSP vial, LOD 2.8% (A); with additional drying in CSP vial; LOD 1.2%, with additional drying in PP containers, LOD 1.2%. (80% SE S-370, 5% total vitamins and 15% MCC)

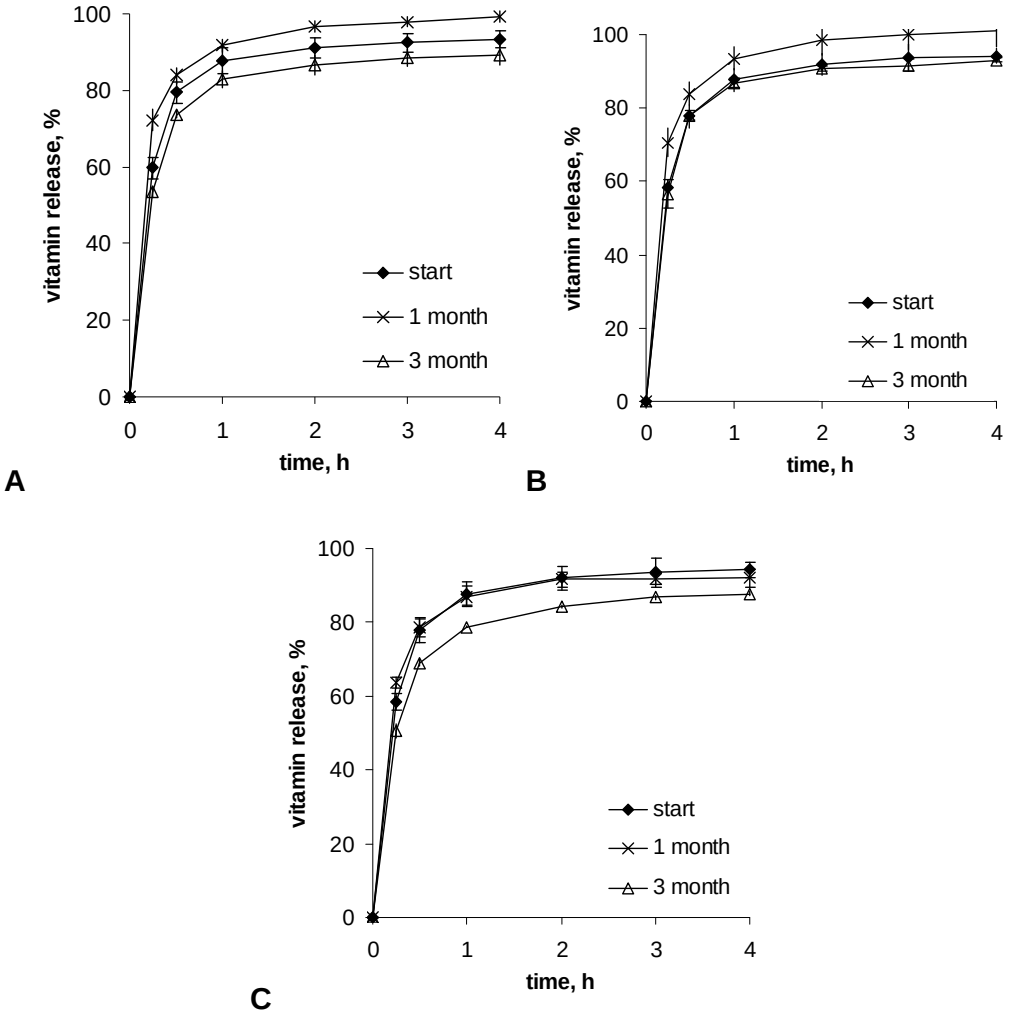


Figure 17.A. Thiamine release from granules obtained by wet granulation stored for 3 month at 25℃/60r.h.. In CSP vial, LOD 2.8% (A); wi th additional drying in CSP vial; LOD 1.2%, with additional drying in PP containers, LOD 1.2%. (80% SE S-370, 5% total vitamins and 15% MCC)

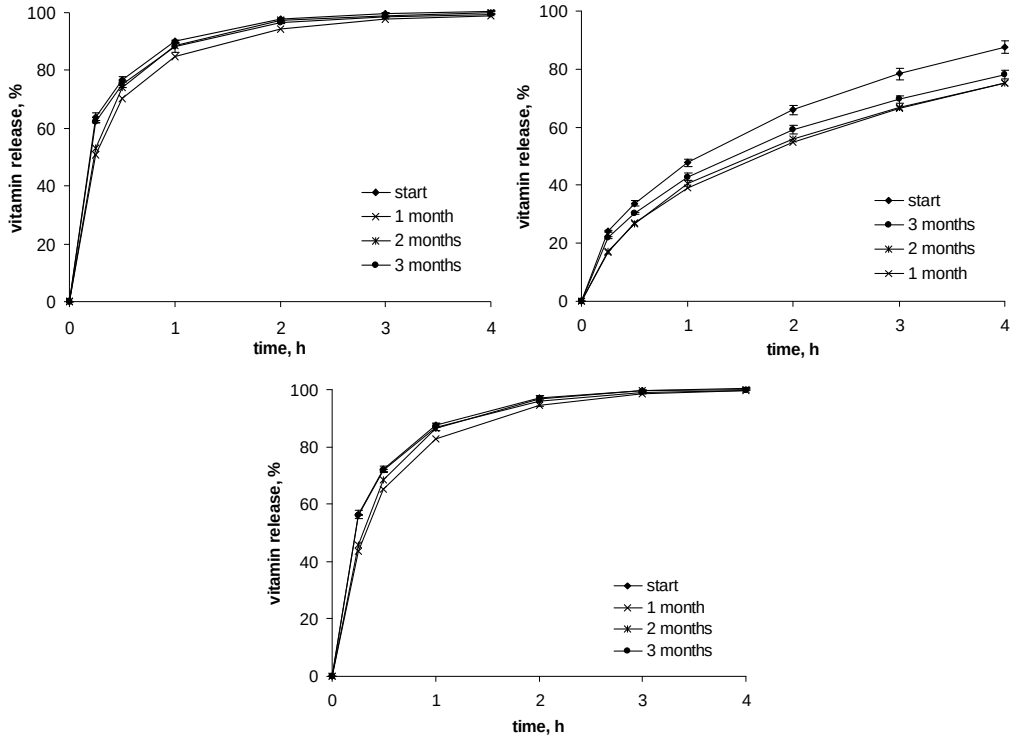


Figure 18.A. Release from granules obtained by melt granulation stored for 6 month in PP containers (80% SE S-1170, 5% total vitamins and 15% MCC), (A) nicotinamide, (B) riboflavin (C) pyridoxine.

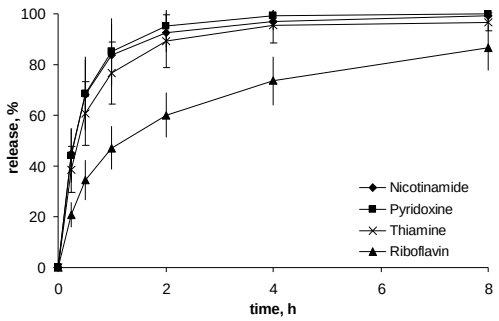


Figure 19.A. Release of vitamins from mini tablets obtained by melt granulation granules containing 20 % SE S-370, 75 % MCC and 5 % vitamins. The tablets disintegrate during dissolution therefore no diffusion coefficients were determined.

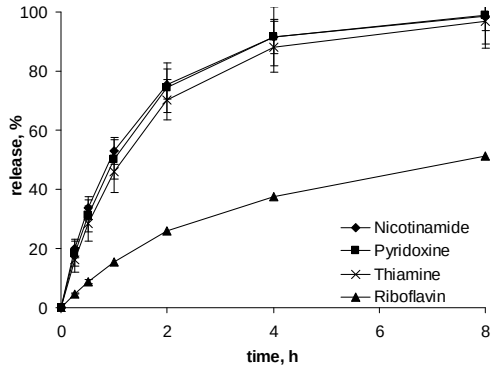


Figure 20.A. Release of vitamins from mini tablets obtained by wet granulation granules containing 80 % SE S-370, 15 % MCC and 5 % vitamins. The granules disintegrate during dissolution therefore no diffusion coefficients were determined.

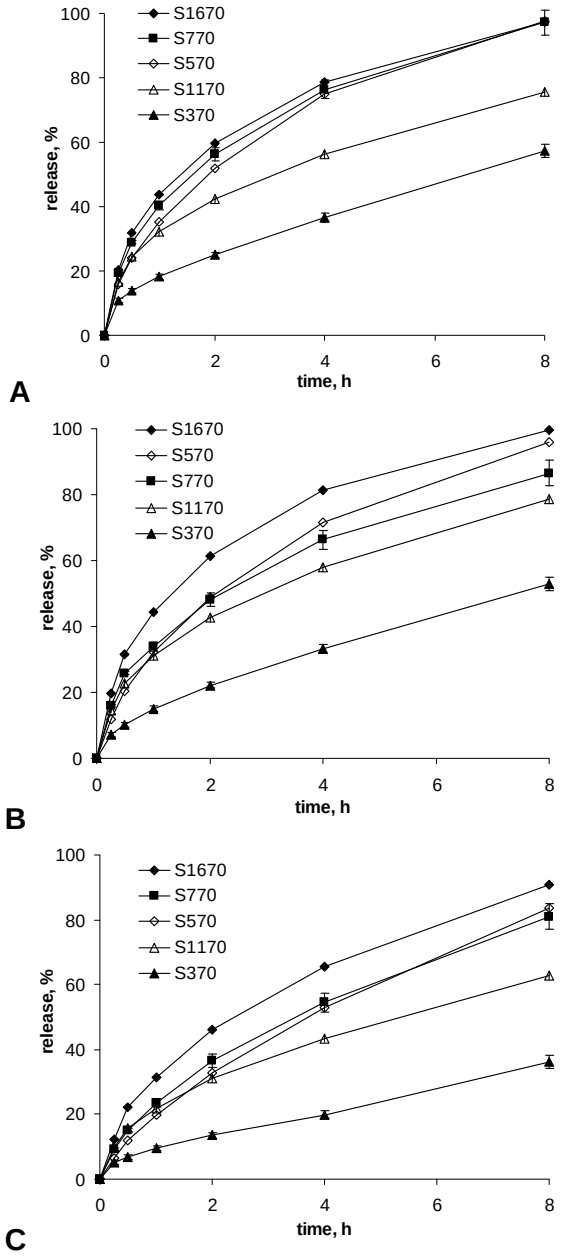
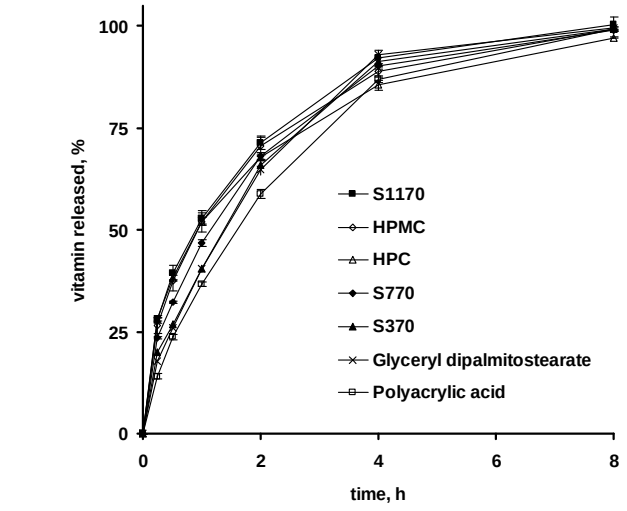
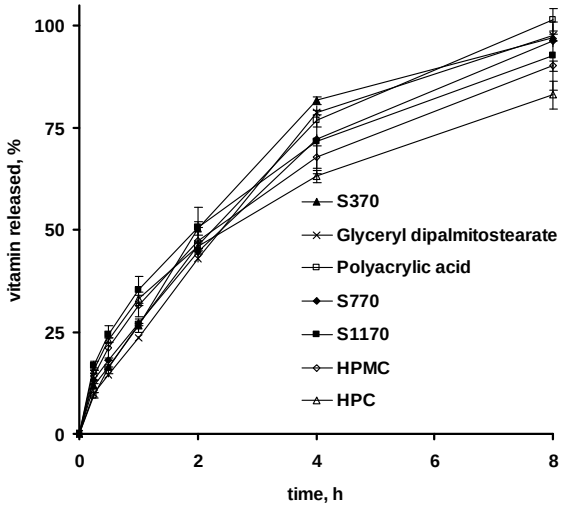


Figure 21.A. Release of vitamins from mini tablets obtained by melt granulation granules containing 80 % SE of different types, 15 % MCC and 5 % vitamins. The release of nicotinamide (A), pyridoxine (B) and riboflavin-5'-phosphate (C) is shown.



A



B

Figure 22.A. Release of vitamins from mini tablets, granules obtained by compression & grinding containing 50 % matrix former, 40 % MCC and 10 % vitamins. The release of pyridoxine (A) and riboflavin-5'-phosphate (B) is shown.

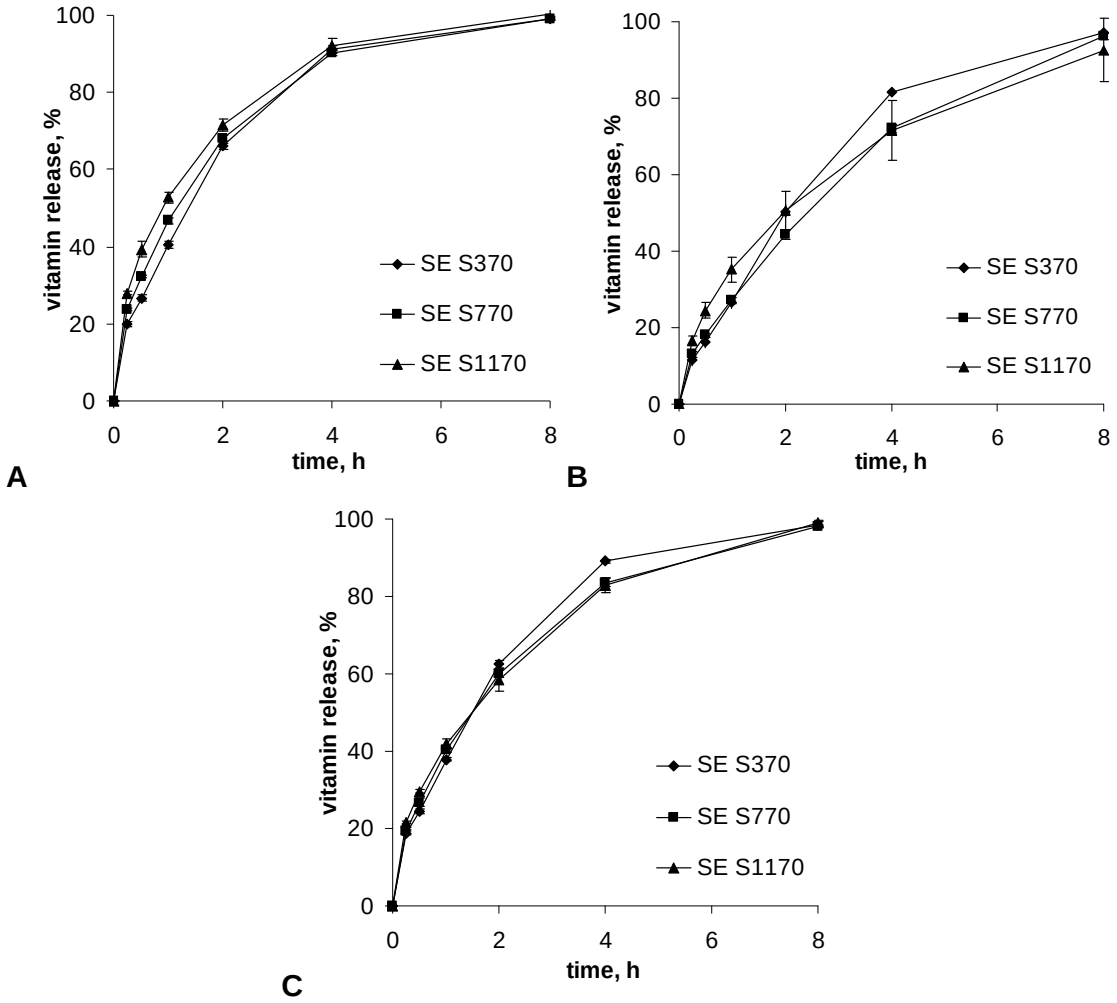


Figure 23.A. Release of vitamins from mini tablets, granules obtained by melt granulation containing 50 % matrix former, 40 % MCC and 10 % vitamins. The release of pyridoxine (A), riboflavin-5'-phosphate (B) and thiamine (C) is shown.

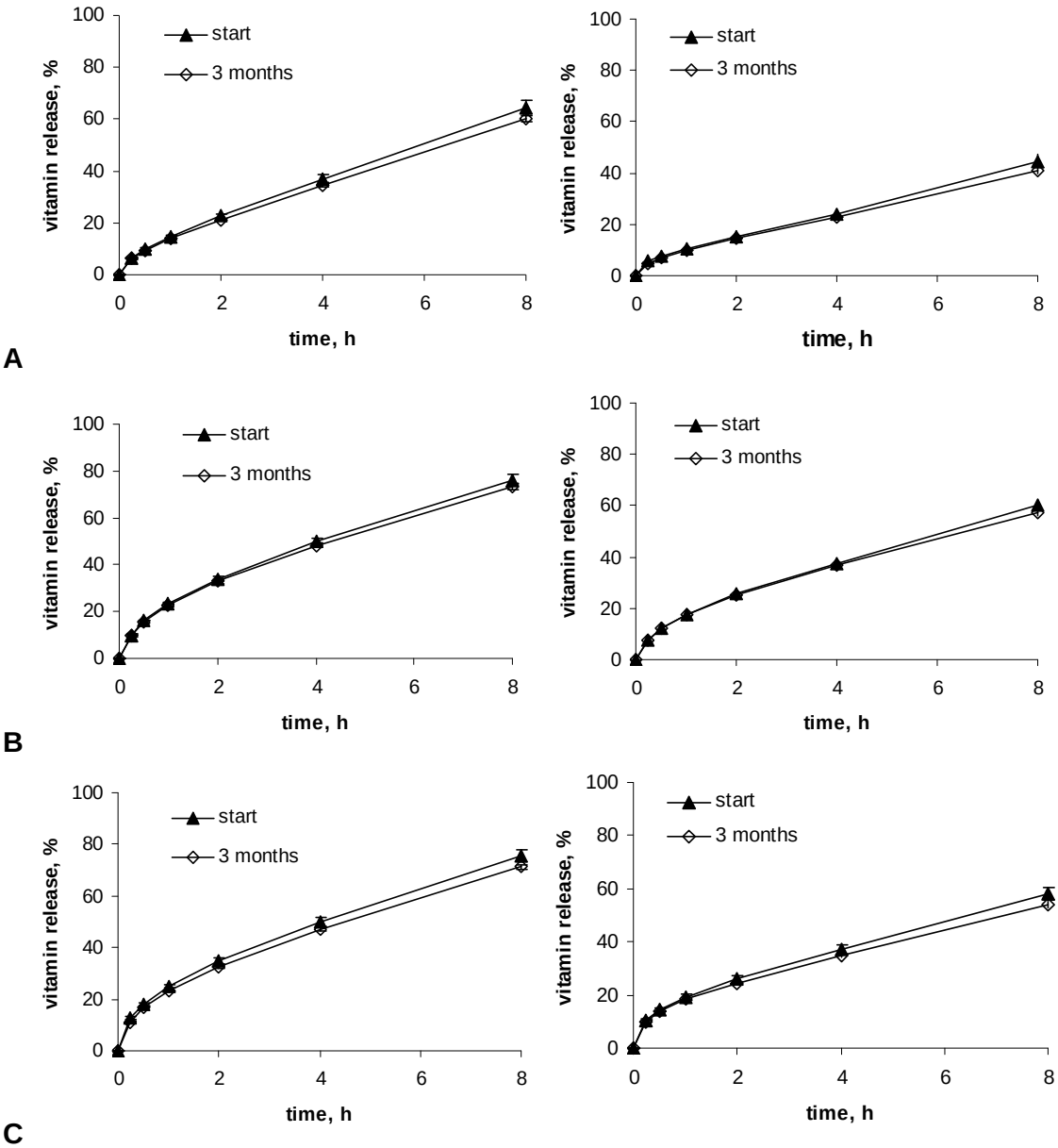


Figure 24.A: Effects of the storage time on pyridoxine, riboflavine and thiamine release from mini tablets into phosphate buffer pH 6.8 after manufacturing and after 3 month at 25 ℃/60 % r.h. Total vitamin content 10 % (left column) or 20% (right column) of the matrix weight. Riboflavin (A), pyridoxine (B), thiamine (C). (Composition of the matrix was kept constant at SE S-370 80 %, 20% MCC, stored in PP containers).

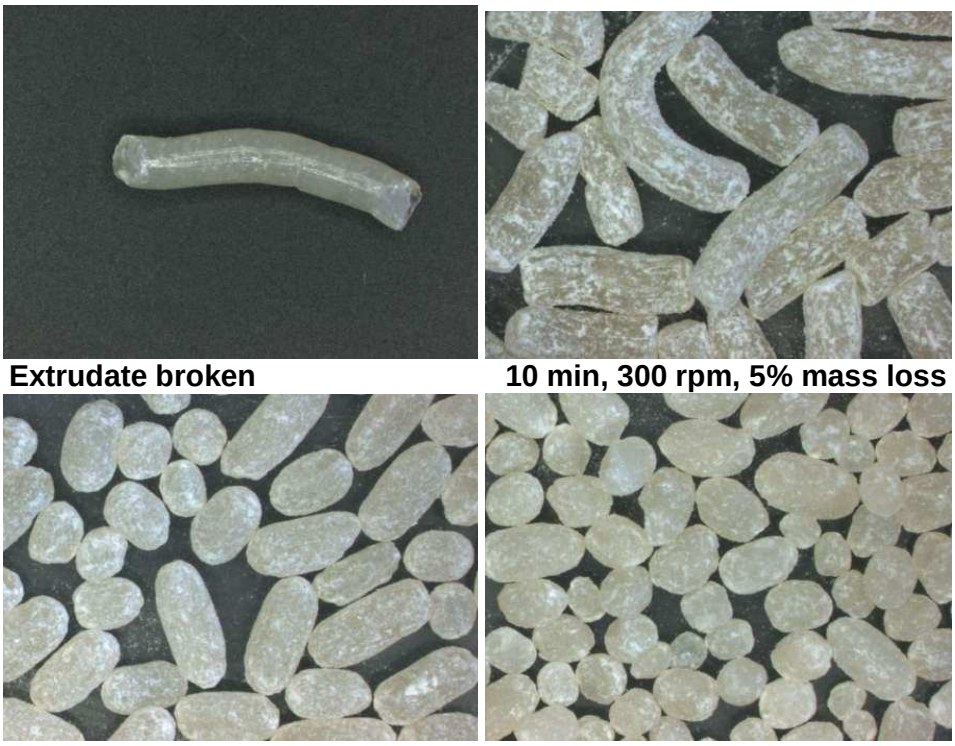


Figure 25.A. Pure SE S-770 extrudates manually broken into short pieces and subsequently spheronized at different rotation speeds for 10 min.

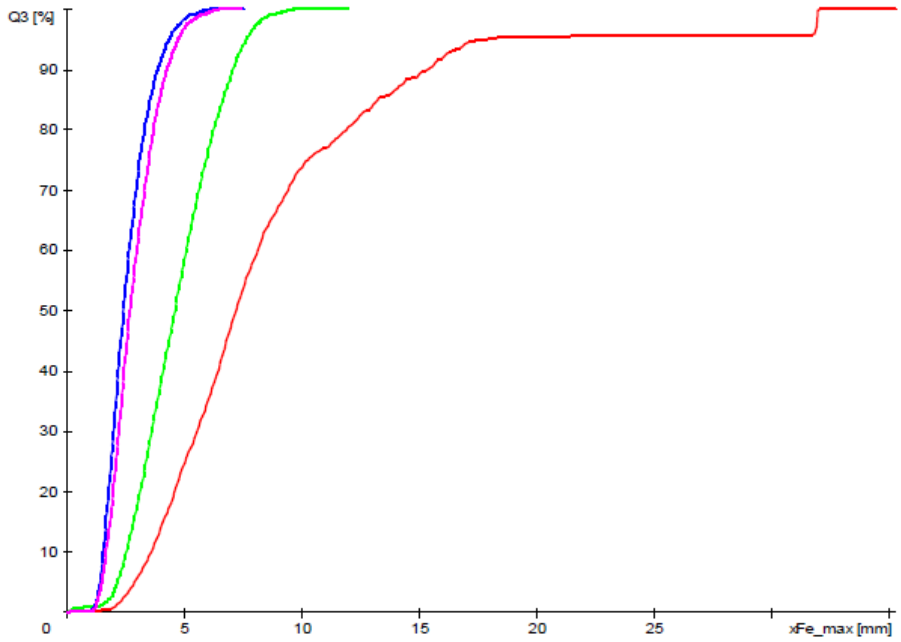


Figure 26.A. Particle size distribution of pellets obtained from SE S-770 without any additives spheronized for 10 min at 900 rpm(pink line), 600 rpm (blue line), 300 rpm (green line) and without spheronization (red line) (spheronization at room temperature). Sum curve.

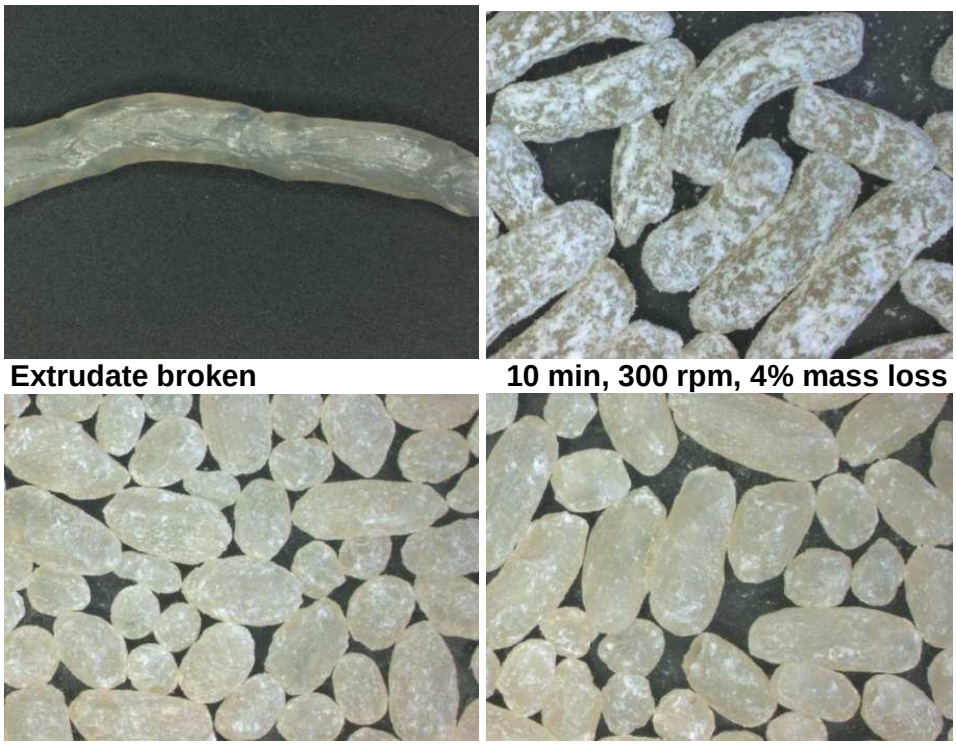
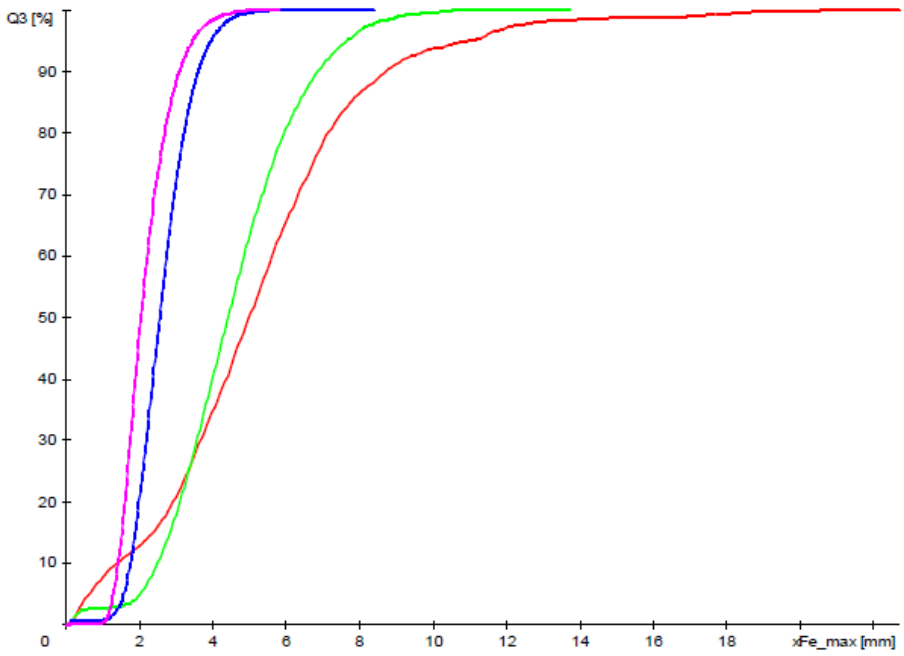


Figure 27.A. Pure SE S-1170 extrudates manually broken into short pieces and subsequently spheronized at different rotation speeds for 10 min.



A

Figure 28.A. Particle size distribution of pellets obtained from SE S-1170 without any additives spheronized for 10 min at 900 rpm(pink line), 600 rpm (blue line), 300 rpm (green line) and without spheronization (red line) (spheronization at room temperature). Sum curve.

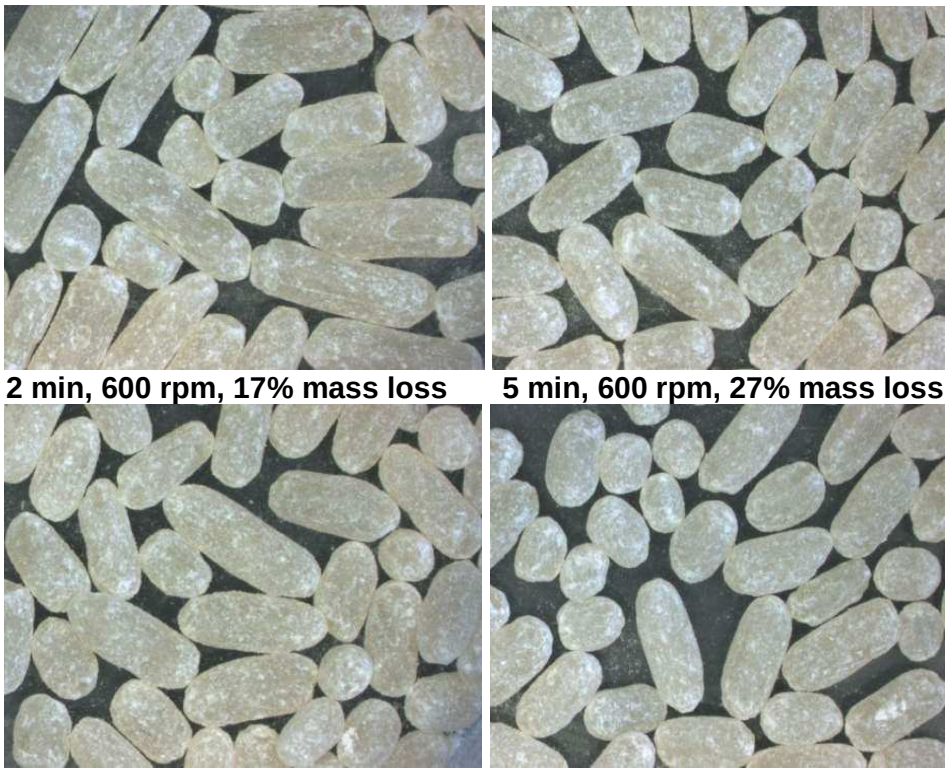


Figure 29.A. SE S-770 pellets spheronized at 600 rpm for different durations.

B

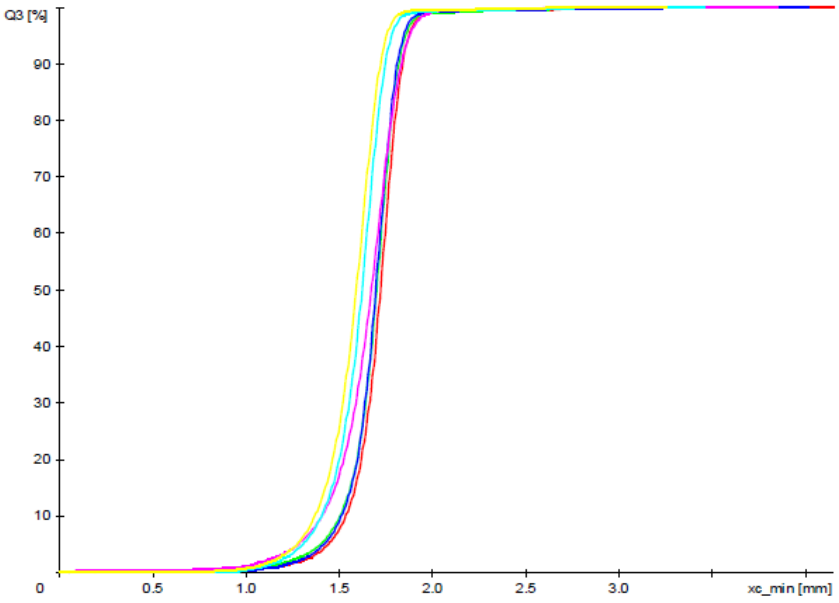


Figure 30.A. Sum curve of diameter of pellets (B) both obtained from SE S-770 without any additives spheronized at 600 rpm for 2 (red line), 5 (green line), 7 (blue line), 10 (pink line), 15 (light blue line) and 20 min (yellow line) (spheronization at room temperature).

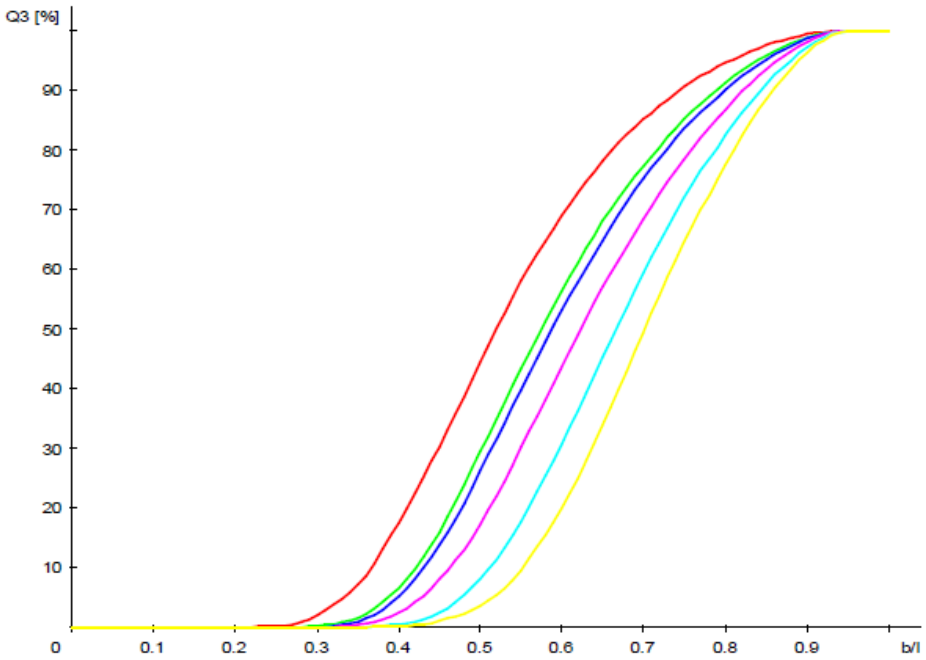


Figure 31.A. Diameter/length ratio of extrudates and pellets consisting of pure SE S-770 spheronized at 600 rpm for 2 (red line), 5 (green line), 7 (blue line), 10 (pink line), 15 (light blue line) and 20 min (yellow line) (spheronization at room temperature).

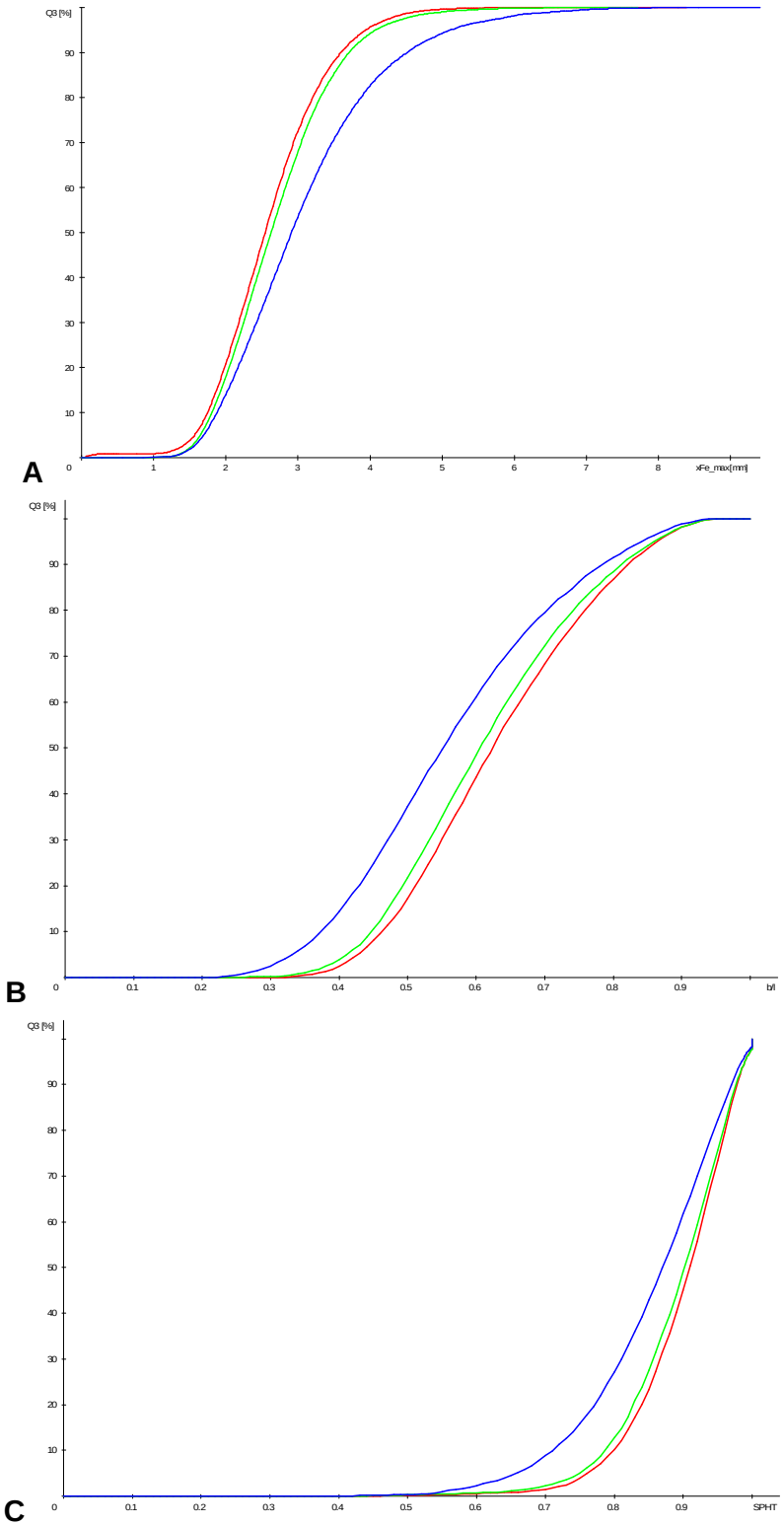


Figure 32.A. Influence of spheronizer temperature on the breaking pattern of the extrudates. Pellets were spheronized for 10 min at 600 rpm consisting of pure SE S-770. Spheronizer temperature: room temperature (~25 ℃) (red line), 40℃(green line) and 60℃ (blue line).(A) sum curve of length of the pellets, (B) diameter/length ratio, (C) sphericity, all calculated from FE_{max}.

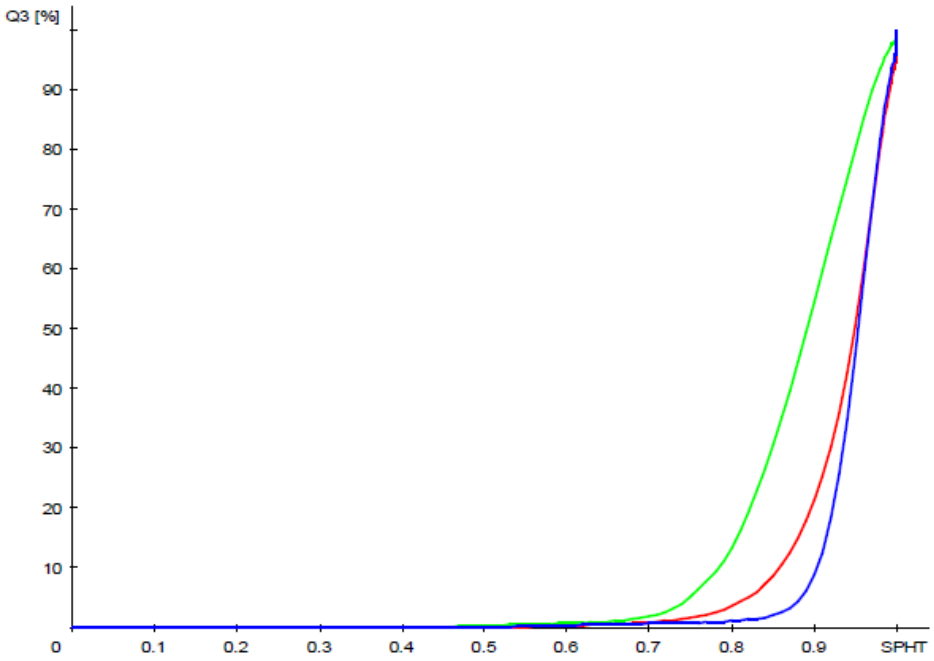
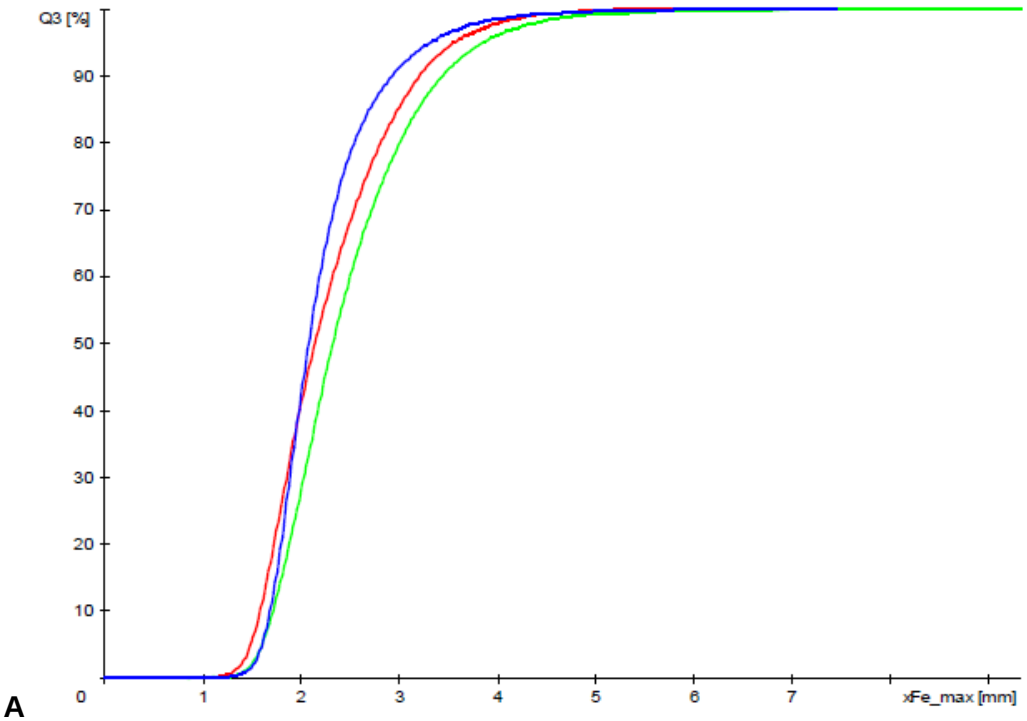
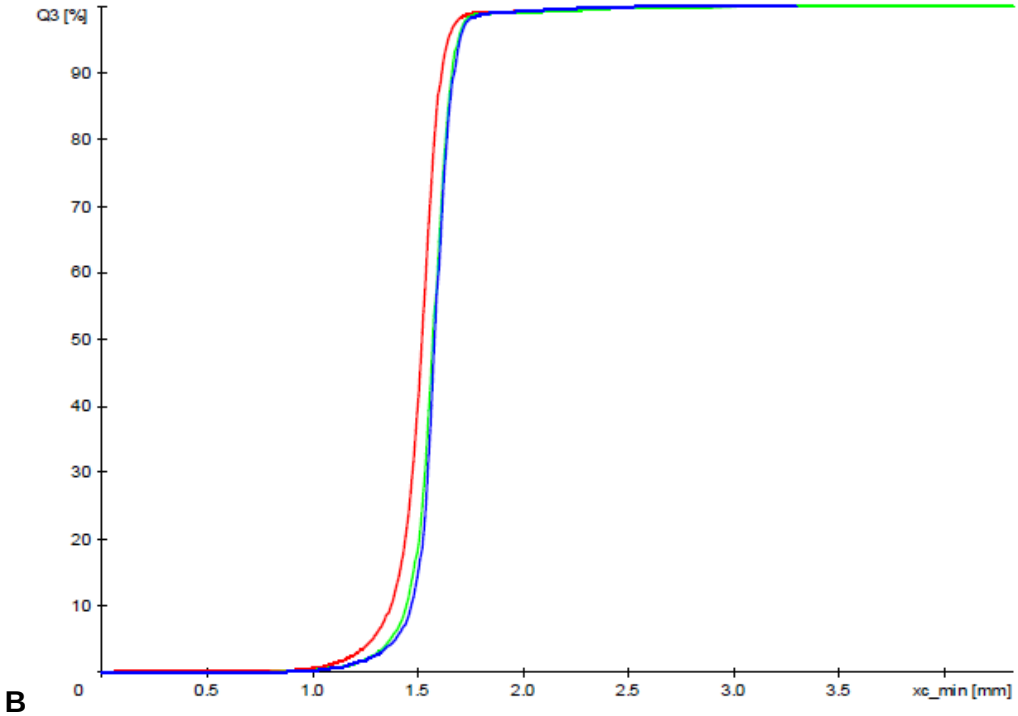


Figure 33.A. Shape characteristics of pellets obtained by different pelletizing methods. Oszillating sieve (red line), ball mill (green line) and simulated pelletizer (blue line) containing 80 % SE S-1170, 15 % tricalcium phosphate and 5 % vitamins. Sphericity, both calculated from Fe_{max}.



A



B

Figure 34.A. Sum curve of pellet length (A) and diameter (B) containing 70-90 % SE S-770, 5-25 % PEG 6000, and 5 % vitamins. Red line: 5 % PEG 6000/ 90 % SE, green line: 15 % PEG 6000/ 80 % SE, blue line: 25 % PEG 6000/ 70 % SE.

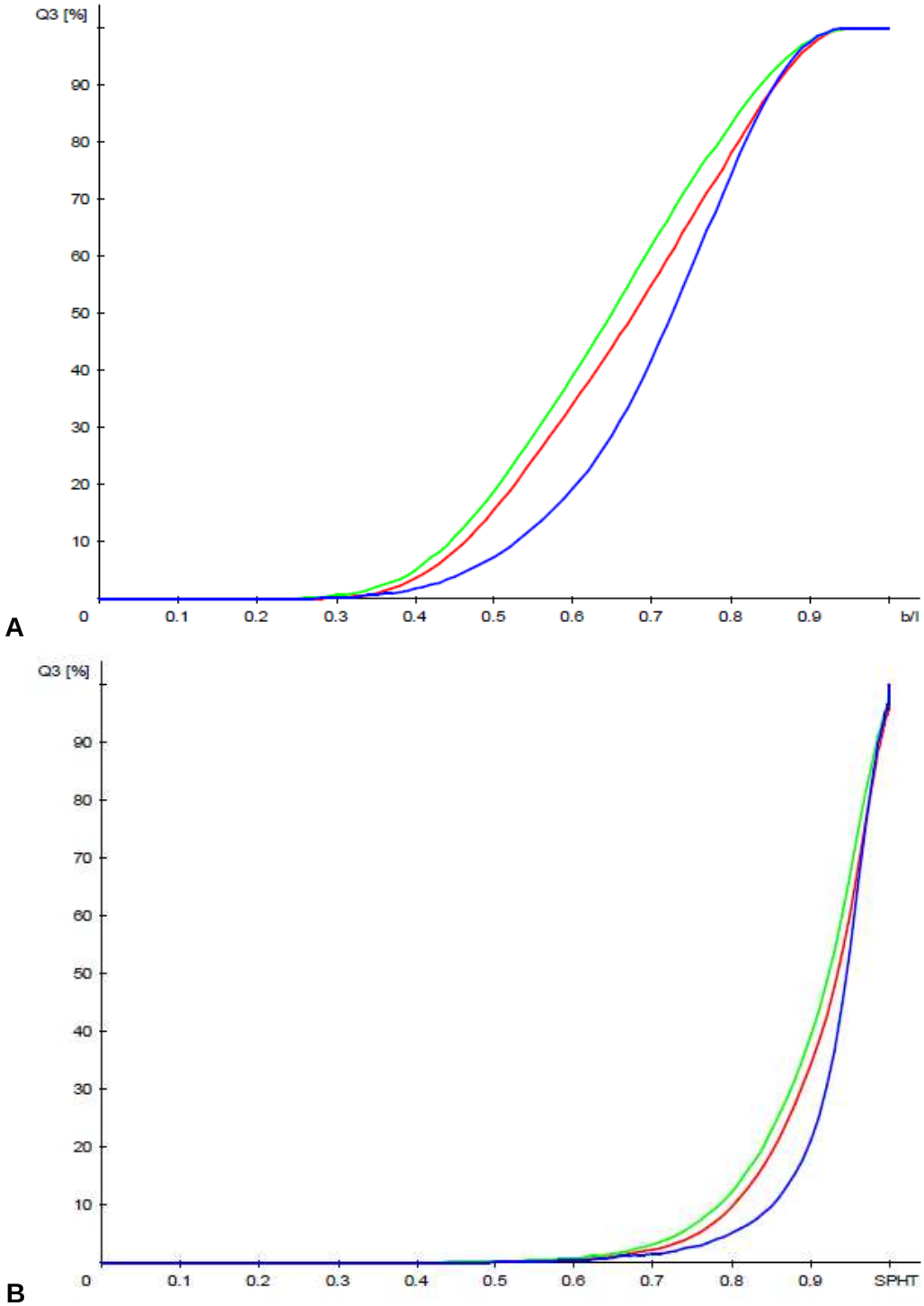
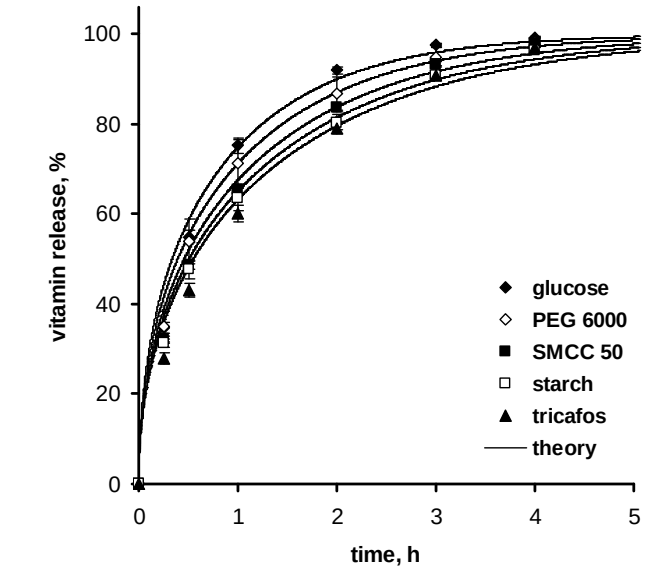
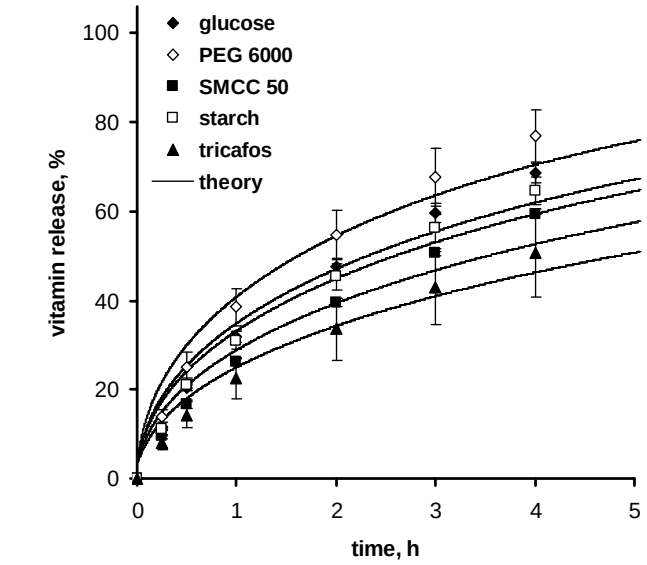


Figure 35.A. Shape characteristics of pellets containing 70-90 % SE S-770, 5-25 % PEG 6000, and 5 % vitamins (A) diameter/length ratio and (B) sphericity, both calculated from Fe_{max}. Red line: 5 % PEG 6000/ 90 % SE, green line: 15 % PEG 6000/ 80 % SE, blue line: 25 % PEG 6000/ 70 % SE.



A



B

Figure 36.A. Release of nicotinamide (A) and riboflavin (B) from pellets containing different fillers. 80 % SE S-770, 15 % filler, 5 % vitamins.

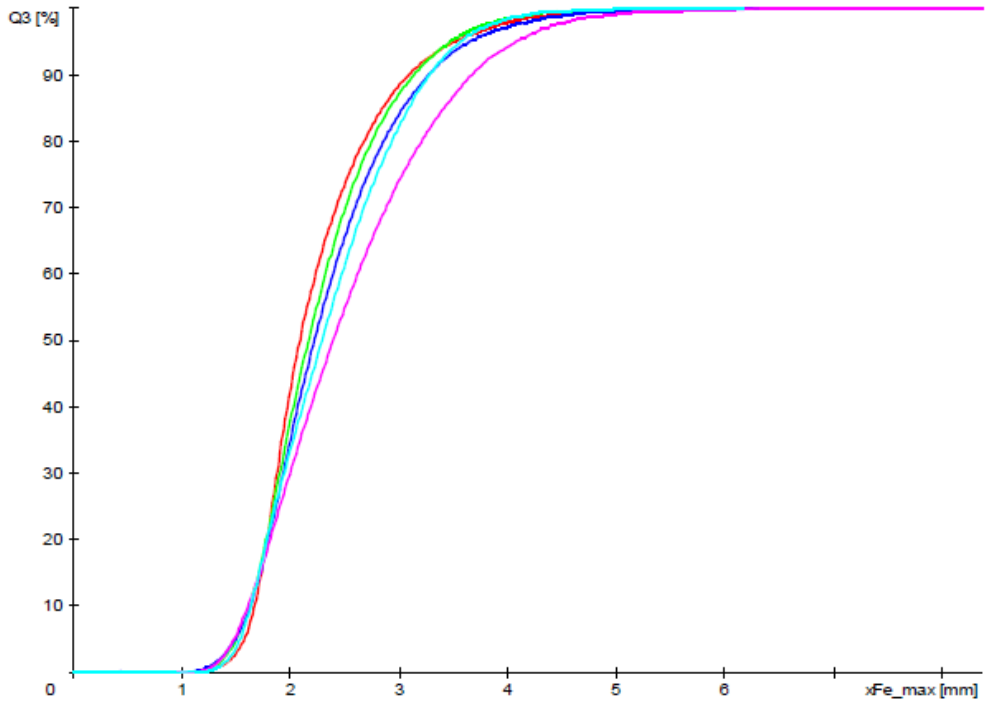


Figure 37.A. Sum curve of pellet length containing 80 % SE S-770, 15 % filler and 5 % vitamins. Filler: SMCC 50 (red line), tricalcium phosphate (green line), PEG 6000 (blue line), starch (pink line) and glucose (light blue line)

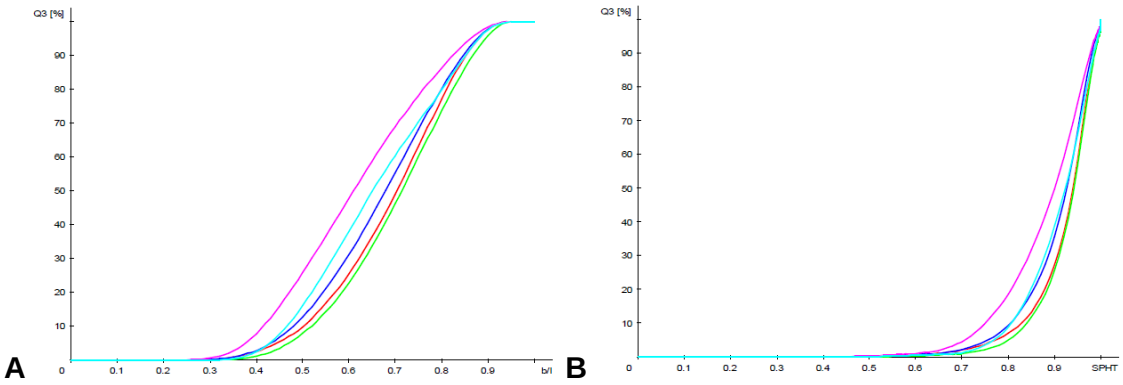


Figure 38.A. Shape characteristics of pellets containing 80 % SE S-770, 15 % filler and 5 % vitamins. Diameter/length ratio and (B) sphericity, both calculated from Fe_{max}. Filler: SMCC 50 (red line), tricalcium phosphate (green line), PEG 6000 (blue line), starch (pink line) and glucose (light blue line) (A) diameter/length ratio and (B) sphericity, both calculated from Fe_{max}.

A **B** **C**

Figure 39.A. Pellet formulations containing 20% (A), 50% (B) and 80% (C) SE S-370. Spheronization parameters: A: 500 rpm, 5min, B/C: 500 rpm, 10 min) (5% vitamins, filler microcrystalline cellulose).

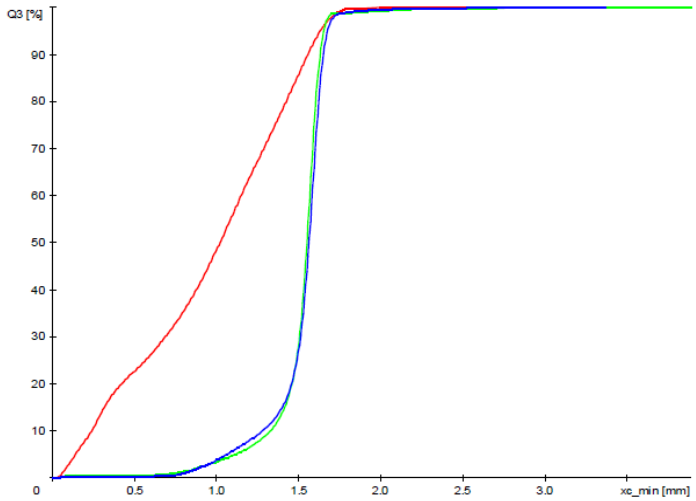


Figure 40.A. Sum distribution of diameter calculated from c_{min} of pellets containing 20 % (red line), 50 % (green line) and 80 % (blue line) SE S-370. Vitamin content 5 %, filler: MCC.

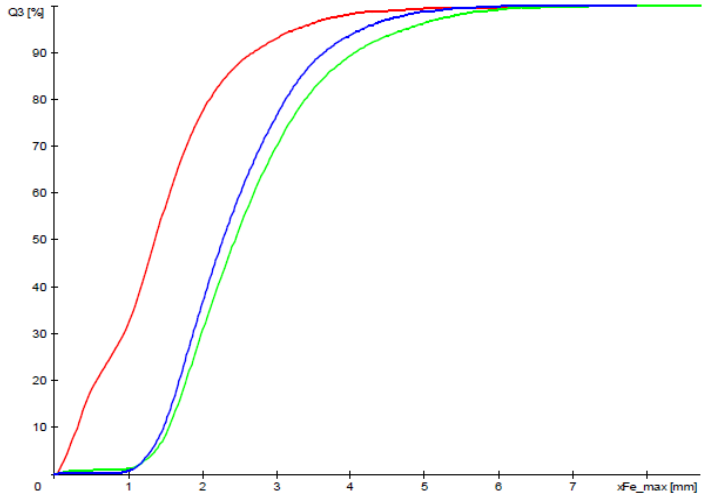


Figure 41.A. Sum distribution of length calculated from Fe_{max} of pellets containing 20 % (red line), 50 % (green line) and 80 % (blue line) SE S-370. Vitamin content 5 %, filler: MCC.

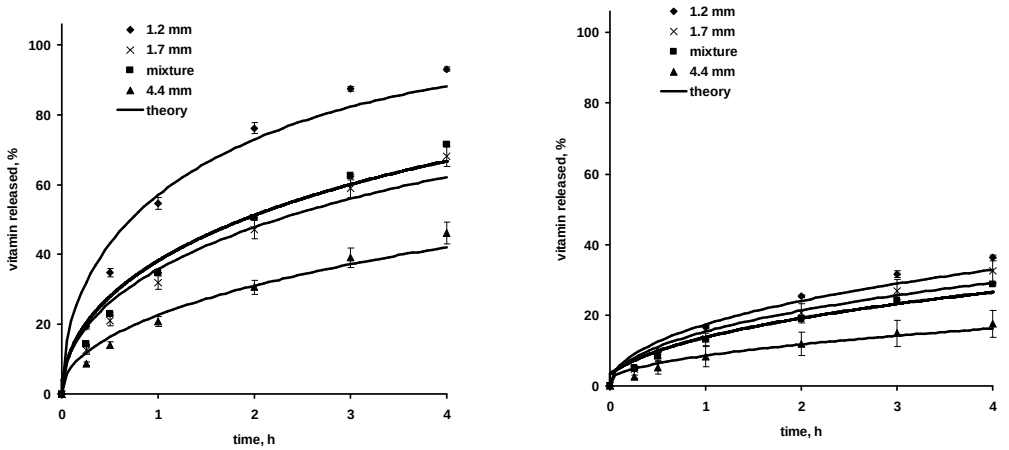


Figure 42.A. Release of pyridoxine (A) and riboflavin (B) from pellets of different size fractions. 80 % SE, 15 % MCC and 5 % vitamins.

Figure 43.A. Pellet formulations containing 80% SE S-370 (A), S-770 (B) and S-1170 (C), 15% MCC 5% vitamins. Spheronization parameters: 1000 rpm, 10min.

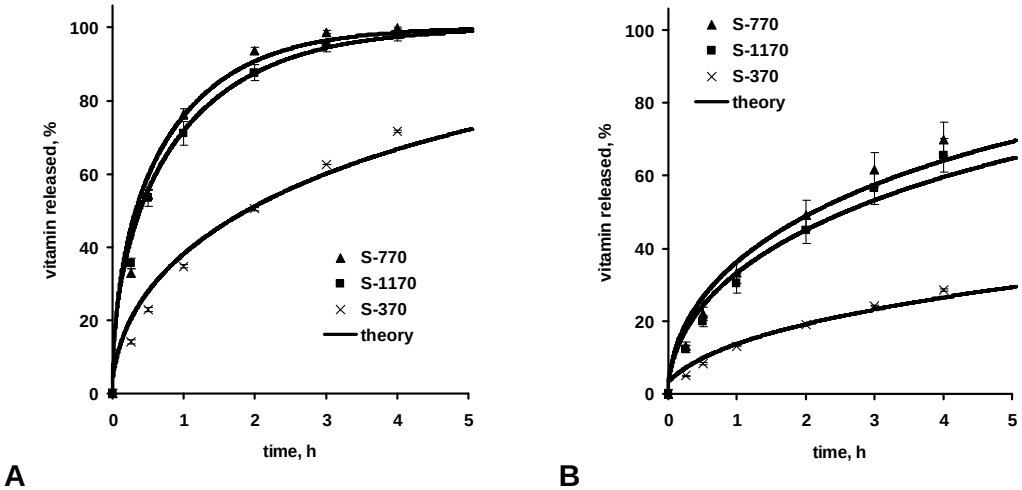
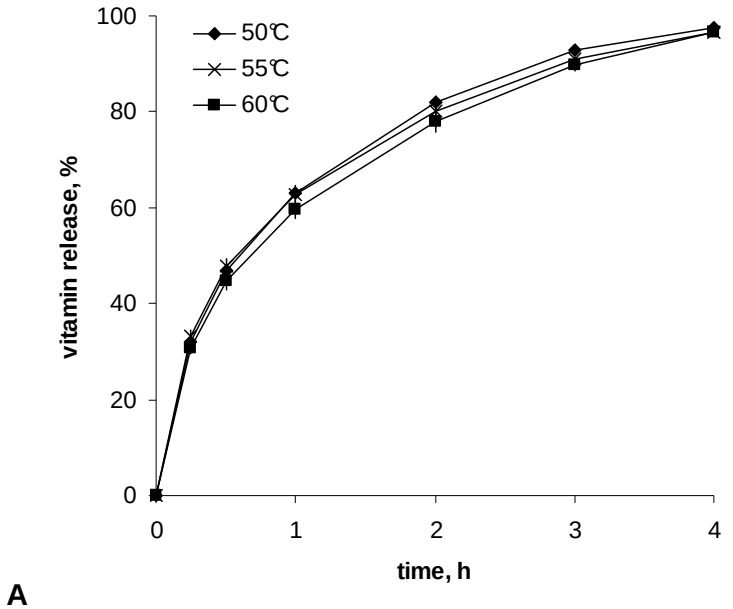
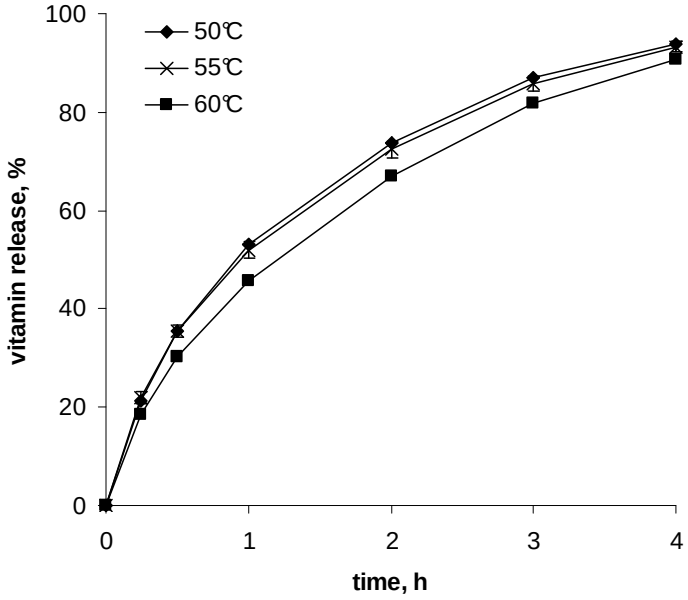


Figure 44.A. Release of nicotinamide (A), riboflavin (B) and pyridoxine (C) from pellets containing different SE types. 80 % SE , 25 % starch and 5 % vitamins.



A



B

Figure 45.A. Release of nicotinamide (A) and thiamine (B) from pellets extruded at different temperatures containing 70 % SE S370, 25 % starch and 5 % total vitamins.

A B C

Figure 46.A. Pictures of SE S-1170 strands extruded with a screw speed of 4 rpm at 50 ℃ (A), 55 ℃ (B) and 60 ℃ (C).

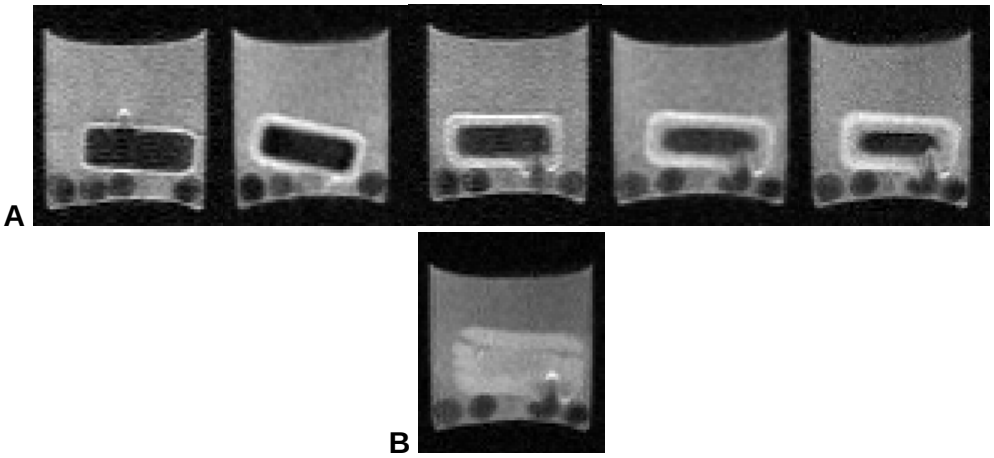


Figure 47.A. NMR images after 10, 30, 50, 70 and 90 min (A) showing the water uptake of SE-based tablets obtained by direct compression. After 14h capping occurs (B).

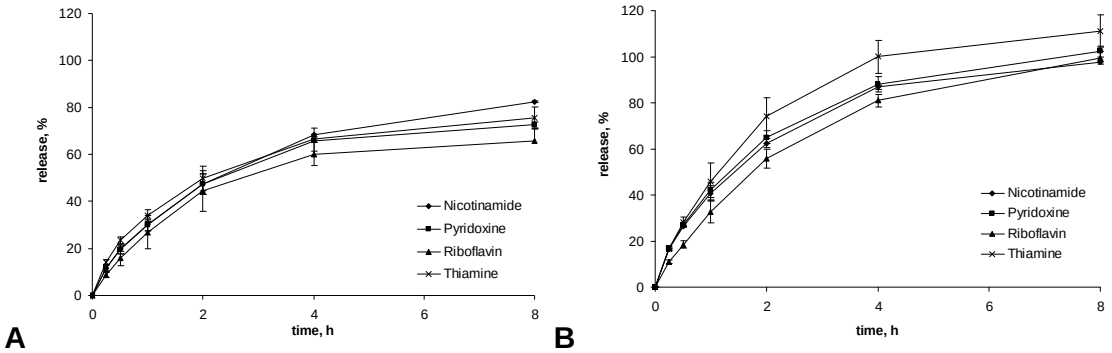


Figure 48.A. Release of multiple vitamins from tablets obtained by direct compression containing 10 % SE S-370, 5% vitamins, 55 % povidone and 30 % MCC. A: untreated sample, B: tempered at 50℃ for 3 h. During dissolution studies capping occurs.

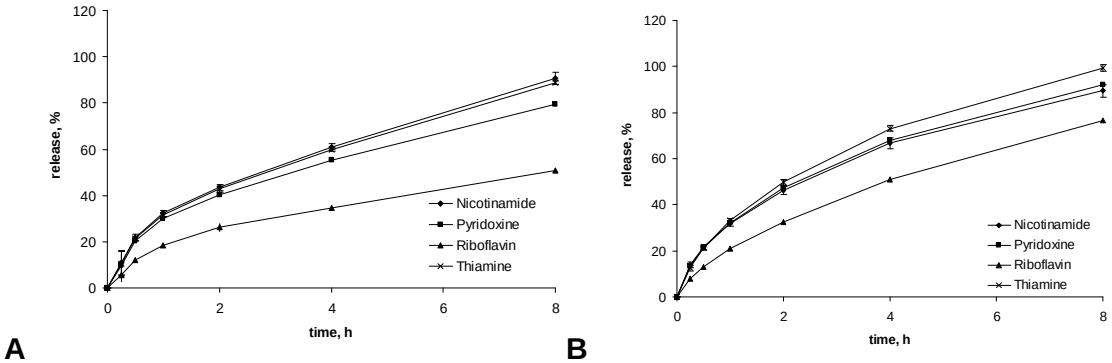


Figure 49.A. Release of multiple vitamins from tablets obtained by direct compression containing 10 % SE S-370, 5% vitamins, 55 % povidone and 30 % SMCC50. A: untreated sample, B: tempered at 50℃ fo r 3h. During dissolution studies capping occurs.

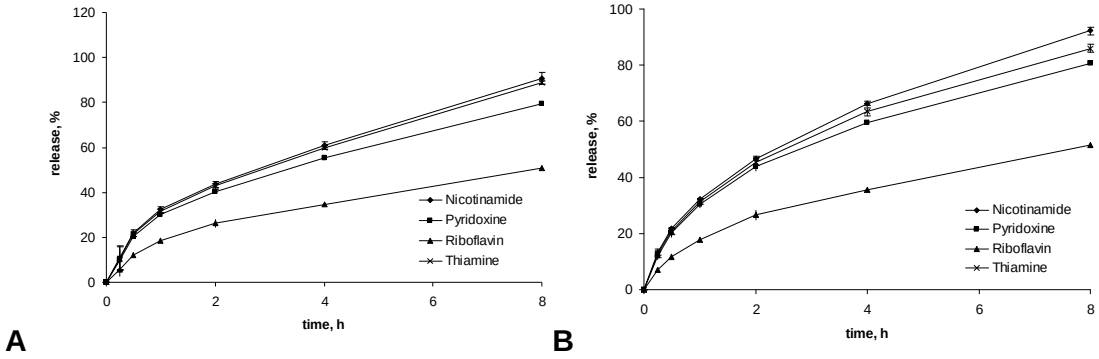


Figure 50.A. Release of multiple vitamins from tablets obtained by direct compression containing 10 % SE S-370, 5% vitamins, 55 % povidone and 30 % SMCC 50 (A) or 30% SMCC 90 (B). During dissolution studies capping occurs.

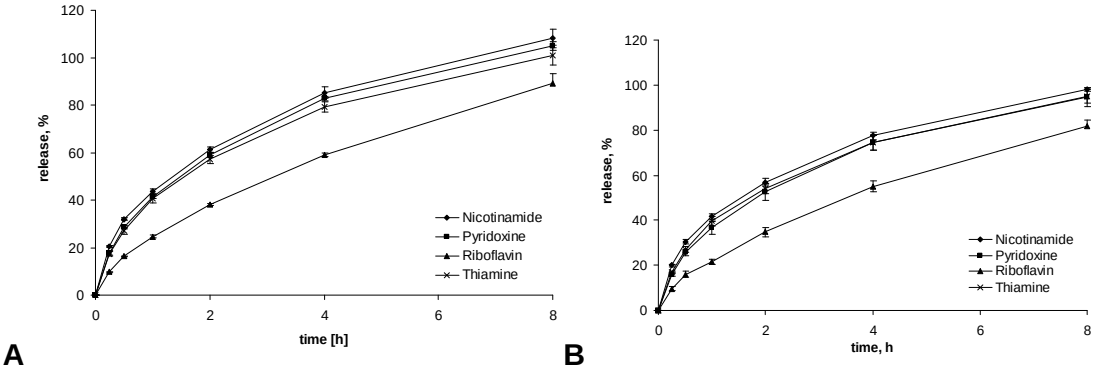


Figure 51.A. Release of multiple vitamins from tablets obtained by direct compression containing 17 % SE S-370, 8% vitamins, 45 % povidone and 30 % SMCC 50. A: untreated sample, B: tempered at 50℃ f or 4h. During dissolution studies capping occurs.

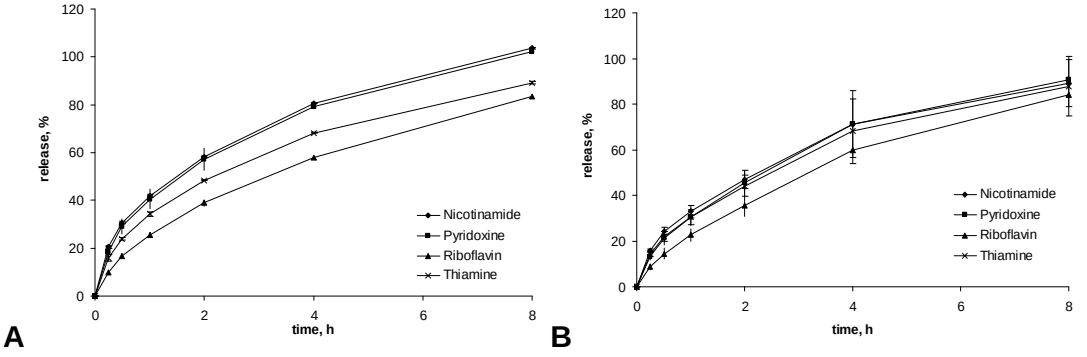


Figure 52.A. Release of multiple vitamins from tablets obtained by direct compression containing 17 % SE S-770, 8% vitamins, 45 % povidone and 30 % SMCC 50. A: untreated sample, B: tempered at 50℃ f or 4h. During dissolution studies capping occurs.

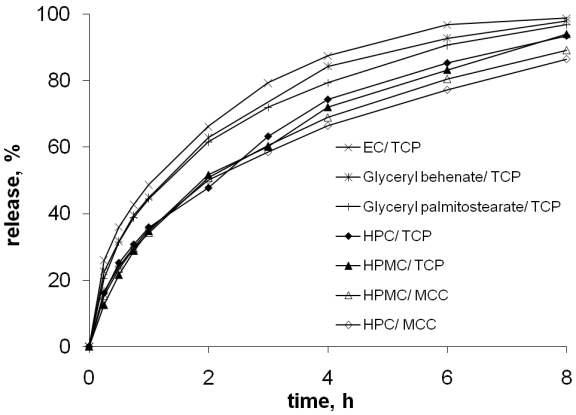


Figure 53.A. Release of pyridoxine from formulations containing different matrix former and fillers in the formulation.

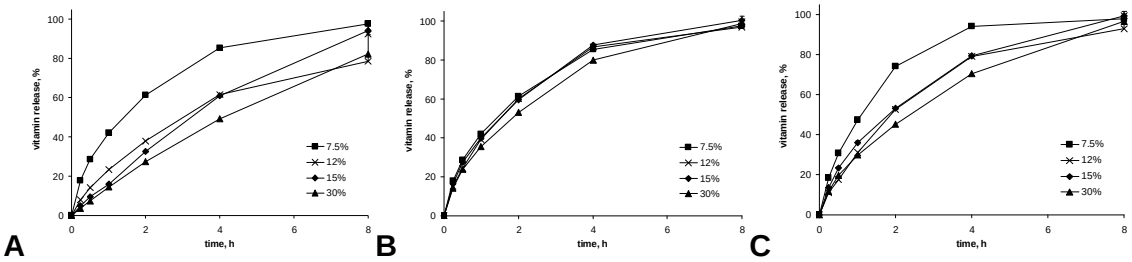


Figure 54.A. Release of riboflavin 5'-phosphate (A), pyridoxine (B) and thiamine (C) from HPMC tablets containing different levels of HPMC K100M (Vitamins incorporated: nicotinamide, pyridoxine hydrochloride, thiamine hydrochloride, riboflavin 5--phosphate, calcium pantothenate and ascorbic acid, other excipients: MCC PH200, povidone, glyceryl dipalmitostearate)

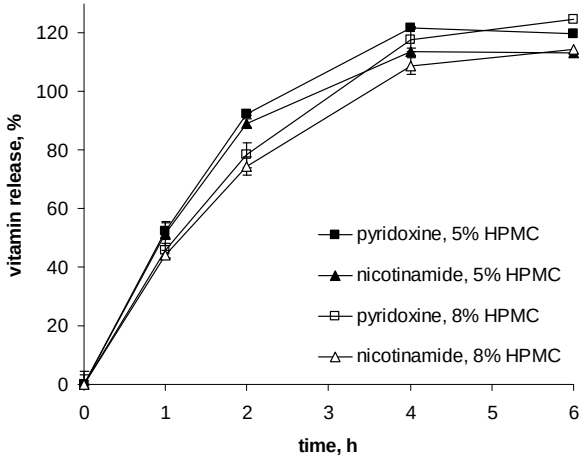
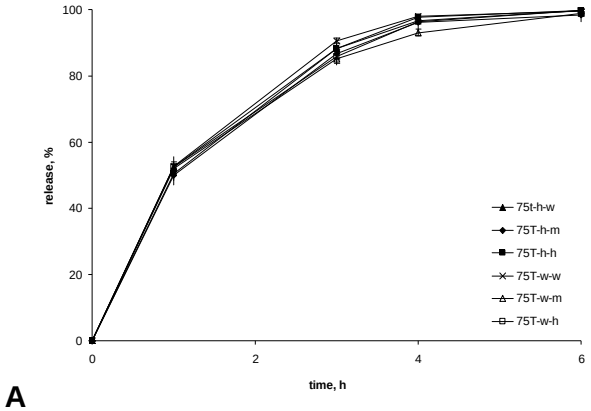
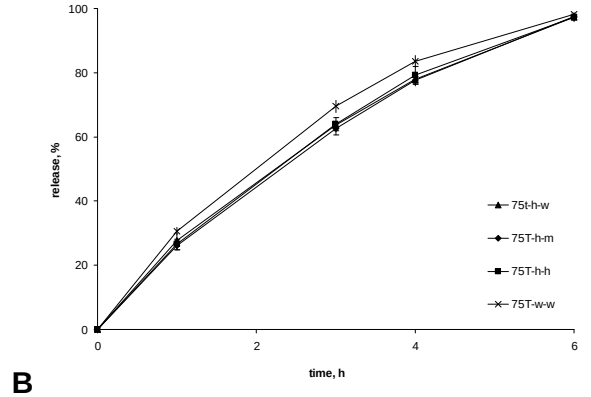


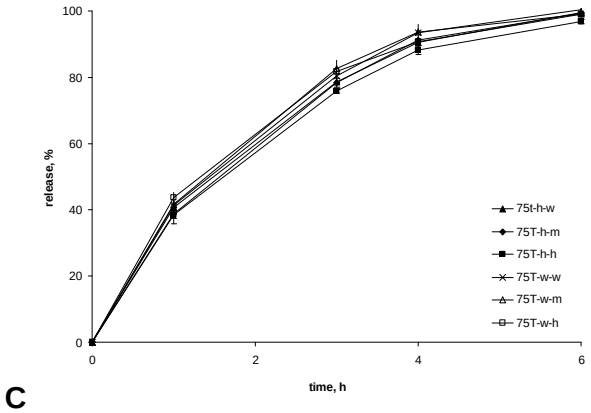
Figure 55.A. Release of nicotinamide and pyridoxine from three layer tablets containing either 5 % or 8 % HPMC K100M as matrix forming agent in the retard layer.



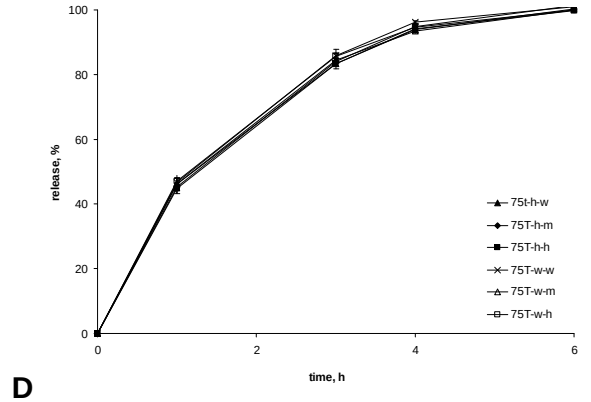
A



B

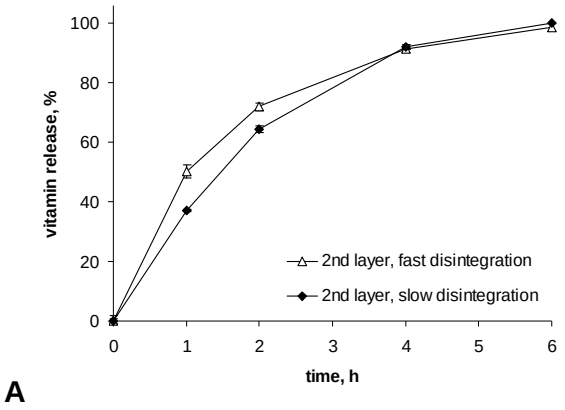


C

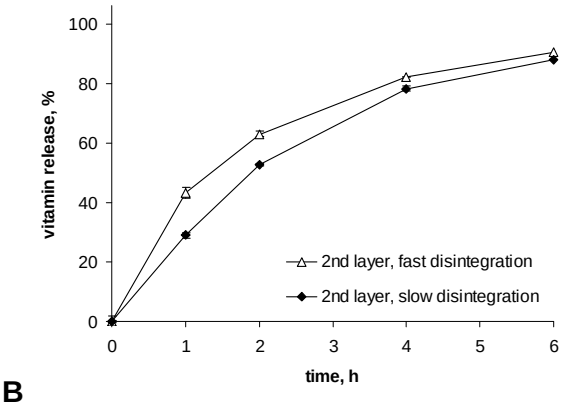


D

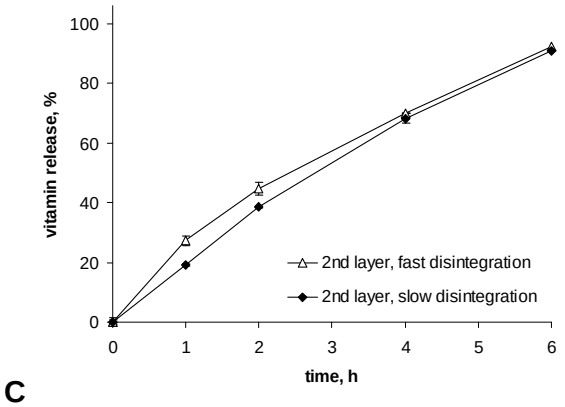
Figure 56.A. Release of nicotinamide (A), riboflavin (B), thiamine (C) and pantothenic acid (D) from three-layer tablets compressed with different compression forces.



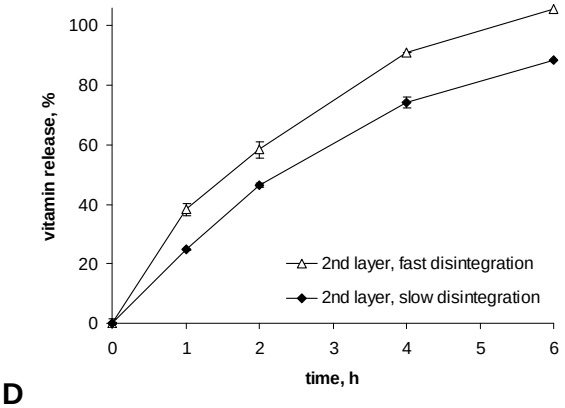
A



B

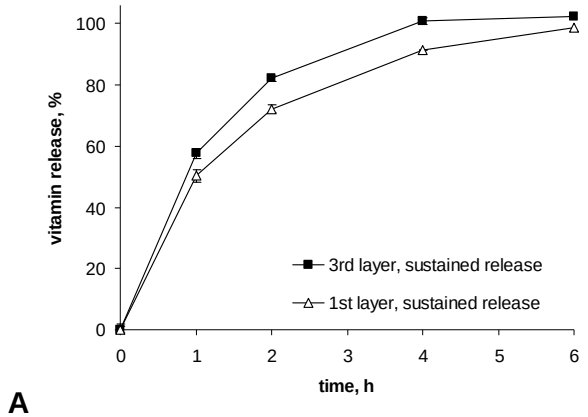


C

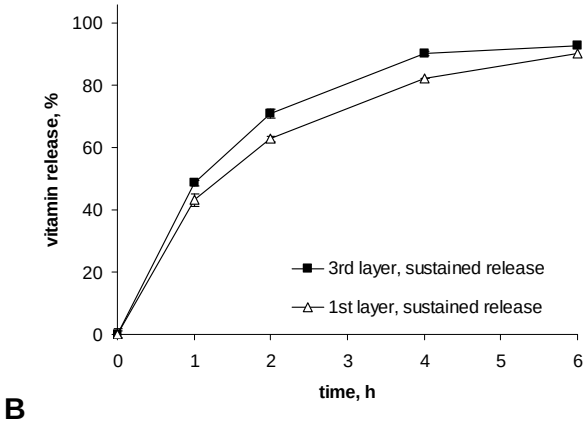


D

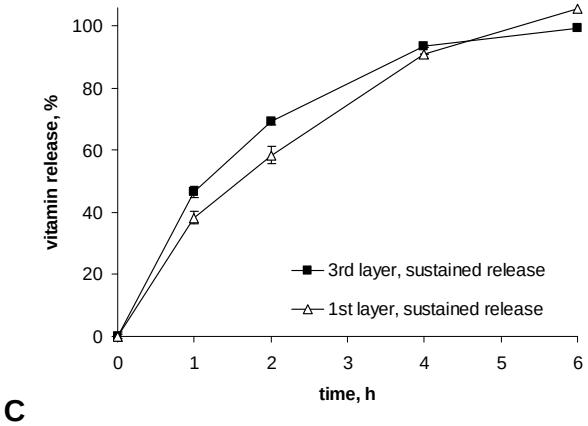
Figure 57.A. Release of ascorbic acid from three-layer tablets containing 8 % HPMC. The second layer disintegrates in 1 min or in 60 min.



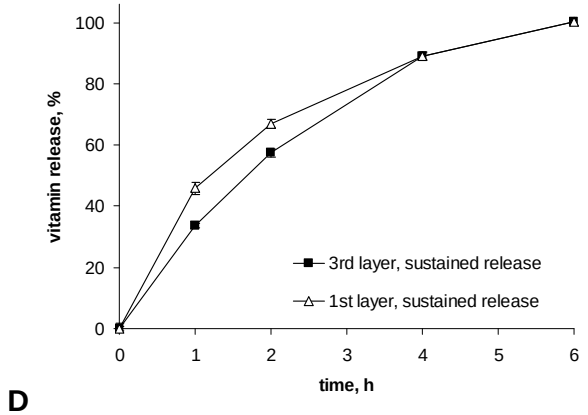
A



B



C



D

Figure 58.A. Release of ascorbic acid from three-layer tablets containing 8 % HPMC. The sustained release layer is either compressed as first or third layer.